PrevaLence of Albuminuria in patients with CARdiovascular Disease and Type 2 Diabetes mellitus in China: a national cross-sectional study PLACARD

Research Protocol

<< Version 3.1 , October 26, 2023 >>

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Sponsor: Heart Health Research Center

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Principal Investigator Statement

I have read the following research protocol:

Research protocol title: Prevalence of Albuminuria in patients with Cardiovascular Disease and Type 2 Diabetes mellitus in China: a national cross-sectional

Version and date: Version 3.1, October 26, 2023

I have read the study protocol and all study documents and agree that they contain all necessary details to conduct the study. I will follow the protocol and complete the research within the allotted time. I will provide a copy of the study protocol and all relevant information to all principals and sub-centre investigators assisting with the conduct of the study. I will discuss the material with them to ensure they fully understand the mission and conduct of the study.

Investigator's signature:

main researcher:

Professor Ma Changsheng _____

date signature

Research Protocol Overview

Study title	Prevalence of Albuminuria in patients with Cardiovascular Disease and Type 2 Diabetes mellitus in China: a national cross-sectional
Research objectives	**Primary Objective** To assess the prevalence of albuminuria in patients who are combined with type 2 diabetes mellitus and different cardiovascular diseases in inpatient and outpatient cardiology departments of secondary and tertiary hospitals in China. **Secondary Objectives** (1) To evaluate the levels of microalbuminuria and macroalbuminuria of patients with type 2 diabetes mellitus (T2DM) in inpatients and outpatients cardiology departments; (2) To evaluate the prevalence of microalbuminuria and macroalbuminuria in patients with T2DM complicated with different cardiovascular diseases; (3) To evaluate the related influence factors of albuminuria and the treatment patterns of CKD patients and non-CKD patients in cardiology departments; (4) To evaluate the management of risk factors and complications in cardiovascular departments of patients with T2DM complicated with microalbuminuria and macroalbuminuria in different levels of hospitals. **Exploratory Objective**

	To evaluate the prevalence of retinopathy in T2DM patients with different cardiovascular diseases attending inpatient and outpatient cardiology departments in secondary and tertiary hospitals in China.
Research design	**Multicenter, cross-sectional study**
Research center	**30 medical centers nationwide in China**
Research sample	**3,000 cases**
Study timeline	**Expected enrollment date of the first patient is December 2023** **Last patient expected completion date is June 2024**
Inclusion criteria	1. Age ⩾18 years old; 2. Diagnosed T2DM combined with ⩾1 CVD (hypertension, coronary heart disease, atrial fibrillation, heart failure); 3. During the data collection period, they went to the outpatient clinic of the cardiology department of the research center, or received treatment in the cardiology department; 4. Ability to self-sign informed consent (electronic /paper).
Exclusion criteria	1. Pregnant or lactating women; 2. Dialysis patients; 3. Other diseases that lead to elevated albuminuria, such as severe infection, confirmed primary glomerular disease, etc.;

	4. Malignant tumors being treated (surgery, chemotherapy, radiotherapy or targeted therapy); 5. Cachexia (CSS score ⩾ 5 points); 6. Severe liver disease (Child- Pugh grade C) ; 7. Participated in an interventional clinical trial in the past three months.
Statistical methods	The analysis will be performed using SAS 9.4 statistical software. Descriptive statistics will be calculated and reported, including number of observations, means, standard deviations, medians, interquartile ranges for continuous variables, and frequencies and percentages for categorical variables. Percentages will be calculated based on non-missing data unless otherwise specified. The data will be checked for bias and outliers. Conversion will be done as needed. Missing data will be assumed to be missing at random or completely at random, and no imputation will be applied except in special circumstances.
Data collection	Case Report Form (CRF)

1 Introduction and Research Background

1.1 Cardiovascular disease, type 2 diabetes and chronic kidney disease

The association between Cardiovascular Disease (CVD) and Chronic Kidney Disease (CKD) is well established. Traditional risk factors for CVD and CKD are similar, with type 2 diabetes mellitus (T2DM) being the most prevalent risk factor. However, CKD is underdiagnosed and undertreated in patients with CVD. Further understanding of the combination of CKD in CVD patients is important to formulate prevention and treatment strategies for CVD patients and high-risk groups, reduce adverse events in CVD patients, and prevent progression of CKD to End Stage Renal Disease (ESRD).

CVD patients and CVD high-risk patients are high-risk groups for CKD. The Spanish MULTIRISC study showed that about 37% of outpatients with CVD and CVD high-risk patients had CKD[1]. T2DM accounts for 25%-30% of outpatients and inpatients in the department of Cardiology, which is an important reason for the high incidence of CKD in the CVD population. Population aging has not only led to an increase in the prevalence of T2DM but also the prevalence of the comorbid CKD. The greatest increase in the prevalence of T2DM has occurred in low- and middle-income countries, where patients with T2DM are also at higher risk of developing CKD. Although the incidence of CVD in T2DM patients has decreased in recent years, T2DM-related renal impairment has not decreased correspondingly. In China, 20%-40% of T2DM patients will progress to CKD, which is the main factor of CKD and ESRD[2]. Globally, more than 50% of patients requiring renal replacement therapy have concurrently T2DM[3].

Impaired renal function increases the risk of CVD by 2 to 4 times[4] and T2DM patients with

CKD live an average of 10-16 years shorter than others[5]. In CVD, urinary protein is strongly associated with an increased risk of developing heart failure, especially in patients with T2DM or CKD or both[6]. A recent large study integrated 4 community-based cohorts and investigated the prognostic value of 12 biomarkers (including urinary protein excretion rate, natriuretic peptide, and troponin) in 22,756 participants. With a median follow-up of 12 years, increased urinary protein excretion was found to be an independent predictor of Heart Failure with reduced Ejection Fraction (HFrEF) and Heart Failure with preserved Ejection Fraction (HFpEF) factors, and for each increase standard deviation in Urinary Albumin/Creatinine Ratio (UACR), the risk of HFrEF increases by 21% and that of HFpEF increases by 33%[7]. Increased proteinuria may reflect elevated levels of endothelial function and inflammation, Which is consistent with the widespread microvascular dysfunction and inflammation characterized by HFpEF[8]. Data from the SPRINT study showed that proteinuria had an cumulative predictive value for heart failure risk on the basis of eGFR (estimated glomerular filtration rate)[9]. Decreased renal function is also associated with an increased risk of coronary heart disease. With the eGFR decreased to 60 - 75 mL/min/1.73 m^2, the incidence of coronary heart disease increased linearly. When the eGFR decreased to 15 mL/min/1.73 m^2, the risk of dying from coronary heart disease increased threefold[10]. In addition, albuminuria can also increase the mortality of non-ST-segment elevation myocardial infarction (NSTEMI) patients[11]. Even in the absence of decreased eGFR, patients with elevated UACR had significantly higher CKD and CVD risks[12], while lower urinary protein levels improved cardiovascular and renal outcomes in T2DM patients[13]. Therefore , the 2021 European Society of Cardiology (ESC) cardiovascular prevention

guidelines recommend screening for the progression of atherosclerotic disease and renal disease in all CKD patients with or without T2DM, including monitoring changes in urinary protein[14].

CKD prevention in T2DM patients is to identify high-risk groups and intervene in related risk factors, such as strict control of blood pressure, rational control of blood sugar, adjustment of unhealthy lifestyle, and adoption of kidney protective therapeutic measures[15]. To prevent CVD events in CKD patients, treatment should be initiated in the early stages of CKD. The presence of proteinuria is a predictor of CKD progression and is associated with increased CVD risk, regardless of normal eGFR. According to the current recommendations of the Kidney Disease: Improving Global Outcomes Working Group, the treatment of patients with T2DM should include lifestyle modification as the basic treatment, followed by renin-angiotensin system(RAAS) inhibitors, Sodium-Glucose Cotransporter 2 inhibitors(SGLT-2i), statins and metformin as first-line treatment. For patients at high risk for CKD progression and CVD events, aldosterone receptor antagonists are recommended. The reduction of urinary protein can be used as a sign of effective treatment. A short-term decrease in urinary protein of about 30% after initiation of RAAS inhibition is a better sign for prognosis in patients with CVD and CKD[14].

1.2 Evaluation of renal function

Based on eGFR and proteinuria levels, the KDIGO guidelines divide CKD into 5 eGFR levels and 3 proteinuria stages (Figure 1) to judge the prognosis of patients. eGFR is one of the reliable indicators to reflect renal function, but its clinical use has certain limitations. Firstly, eGFR is calculated based on serum creatinine levels, which are affected by a variety of

factors, including muscle mass, extrarenal excretion, and dietary factors. Secondly, the eGFR formula is established based on population data and is not applicable to all kidney diseases. Furthermore, the presence of CKD as judged by eGFR alone means that 50% of kidney function has been lost[16].

CKD Category				Classification of Albuminuria		
				A1	A2	A3
				Normal and slightly elevated	Moderately elevated	Severely elevated
				<30 mg/g <3 mg/mmol	30-299mg/g 3-29 mg/mol	⩾300mg/g ⩾30mg/mmol
Classification of eGFR (ml/min/1·73m^2)	G1	Normal renal function	⩾90			
	G2	Mild decline	60-90			
	G3a	Mild to moderate decline	45-59			
	G3b	Moderate to severe decline	30-44			
	G4	Severe decline	15-29			
	G5	Renal failure	15			

Figure 1. Classification and prognosis of chronic kidney disease (CKD) according to the 2012 KDIGO guidelines

UACR is a guideline recommended indicator for monitoring the risk of early kidney injury in T2DM and kidney related diseases, which can reflect early kidney disease and kidney injury. UACR measures the ratio of albumin to creatinine in a single urine sample and is a reliable method for monitoring urinary protein excretion[17]. UACR between 30 and300mg/g is defined as microalbuminuria, and UACR>300mg/g is defined massive proteinuria. UACR can reliably reflect the 24-hour urinary protein volume, and is fast, simple, and accurate. It

is an ideal clinical indicator for qualitative and quantitative diagnosis of albuminuria[18]. Thus, given the high cost of CKD treatment and the low cost of detecting albuminuria, as well as the need to identify previously unrecognized patients at high CVD risk, the 2021 ESC Cardiovascular Prevention guidelines recommend that systematic evaluation of urinary protein be considered in all men older than 40 and all women older than 50 (or postmenopausal)[14].

1.3 Improve the awareness rate of kidney disease in CVD patients

However, awareness of CKD has remained low[19]. An international cohort of 3 million patients with diabetes or hypertension found that the overall UACR detection rate for diabetes and hypertension was only 35.1% and 4.1% [20]. A recent Swedish study found that among more than 50,000 patients who met diagnostic criteria for CKD (i.e., at least two eGFR < 60 mL/min/1.73m^2 separated by more than 3 months), only 23% of patients had a diagnosis of CKD in their electronic health records [21]. The NHANES study found that the awareness rate of CKD is much lower than that of hypertension and diabetes[22]. In a NHANES study, the awareness rate of CKD patients with severe renal function decline was 41.8%, while the awareness rate of CKD patients with mild to moderate renal function decline was only 7.8%[23]. In the KEEP study, the awareness rates of patients with the above two conditions were 32.1% and 5.4%, respectively[24]. More importantly, patients with eGFR>60 mL/min/1.73 m^2 and elevated urinary protein account for more than 40% of CKD patients, but urinary protein detection rates were low, and physicians and patients are more aware of this type of CKD [25]. This missed diagnosis may have adverse consequences for

patient care, as the use of nephrotoxic drugs is more common in undiagnosed CKD patients[26]. Therefore, in the Healthy People 2030 plan in the United States, improving the awareness rate of CKD continues to be listed as a priority national public health goal by the health department[27].

In China, the prevalence of albuminuria measurement in CVD patients is still unclear, and there is limited data on the prevalence of albuminuria in patients with T2DM in the Department of Cardiology. Further research is needed to increase relevant data to better guide the diagnosis and treatment of CVD patients.

2. Research objectives

2.1 Primary objective

To assess the prevalence of albuminuria in patients who are combined with T2DM and different cardiovascular diseases in inpatient and outpatient cardiology departments of secondary and tertiary hospitals in China.

2.2 Secondary objectives

(1)To evaluate the levels of microalbuminuria and macroalbuminuria of patients with type 2 diabetes mellitus (T2DM) in inpatients and outpatients cardiology departments;

(2) To evaluate the prevalence of microalbuminuria and macroalbuminuria in patients with T2DM complicated with different cardiovascular diseases;

(3) To evaluate the related influence factors of albuminuria and the treatment patterns of CKD patients and non-CKD patients in cardiology departments;

(4) To evaluate the management of risk factors and complications in cardiovascular

departments of patients with T2DM complicated with microalbuminuria and macroalbuminuria in different levels of hospitals.

2.3 Exploratory objective

To evaluate the prevalence of retinopathy in T2DM patients with different cardiovascular diseases attending inpatient and outpatient cardiology departments in secondary and tertiary hospitals in China.

3 Research design

3.1 Overall design

The PLACARD study was a cross-sectional observational study.

3.2 Center distribution

In the 6 major administrative regions of China (North China, East China, Northeast China, Central South China, Southwest China, Northwest China), 30 regionally representative medical centers with more than 50 daily outpatients in the Department of Cardiology were selected, among which 3 tertiary hospitals and 2 secondary hospitals in each district. According to the comprehensive situation of the hospital, a representative cardiology ward will be selected in the inpatient department of each branch center, and several representative outpatient doctors will be selected in the outpatient department.

3.3 Number of subjects

In this study, 50 patients with T2DM who meet the inclusion and exclusion criteria in the outpatient department of cardiology and 50 inpatients will be continuously included in each sub-center. A total of 100 patients will be included in each sub-center, totaling 3,000

patients. For details on sample size, see 6.6 Sample Size Estimation.

3.4 Estimated study duration

Each sub-center was activated and enrolled in sequence, with the enrollment period from December 2023 to June 2024.

3.5 Patient Participation Time

Patient data will be collected after signing the informed consent, and the data of enrolled patients will be included in the data analysis. No follow-up will be conducted in this study.

3.6 End of study

The study end date is the enrollment date of the 3,000th patient, which is expected to be completed in June 2024.

3.7 Study Population

This study will adopt a stratified, multi-level, and multi-center strategy for continuous screening to enroll patients who meet all inclusion criteria and none of the exclusion criteria. During the enrollment period, the Clinical Coordinator will communicate with and invite all potential patients attending the selected inpatient wards or the designated outpatient physicians. Screening information, including patient name, gender, age, screening time, successful enrollment, and reasons for enrollment failure, will be recorded using the patient screening form (see Appendix 1). The patient screening form is kept by each sub-center, which is the source document of this study and must not be transmitted to anywhere outside the sub-center. Before conducting any study procedures or questionnaires, the research team will obtain electronic or written informed consent from patients.

3.7.1 Inclusion criteria

1. Age ⩾18 years old;

2. Diagnosed T2DM combined with ⩾ 1 CVD (hypertension, coronary heart disease, atrial fibrillation, heart failure);

3. During the data collection period, they went to the outpatient clinic of the cardiology department of the research center, or received treatment in the cardiology department;

4. Ability to self-sign informed consent (electronic /paper).

3.7.2 Exclusion criteria

1. Pregnant or lactating women;

2. Dialysis patients;

3. There are other diseases that lead to elevated proteinuria, such as severe infection, confirmed primary glomerular disease, etc.;

4. Malignant tumors being treated (surgery, chemotherapy, radiotherapy or targeted therapy);

5. Cachexia (CSS score ⩾ 5 points) ;

6. Severe liver disease (Child- Pugh grade C) ;

7. Participated in an interventional clinical trial in the past three months.

4 Research plan

4.1 Study data collection plan

The PLACARD study will be a cross-sectional observational study that collect patient information only once after screening and retrace the case system after the first visit, without any follow-up. It is expected that each center will complete the screening and

enrollment of patients within one month.

During the information collection period the investigator will:

1. Sign the informed consent form: Before signing the informed consent form, the participants should be fully informed of the research purpose and how the data will be used, and the researcher should also sign the informed consent form. The investigator and the patient each keep an original signed informed consent form;

2. Patient screening form: After signing the informed consent form, it will be confirmed whether the patient meets all the inclusion criteria and not all exclusion criteria, and the screening information will be recorded in the patient screening form. In order to ensure the continuity of screening, the screening information of potential patients who failed to enroll will also be recorded in the patient screening form;

3. After the patients are enrolled, the researchers should complete the following tasks and collect relevant data:

- Demographic information: gender, date of birth, education, type of medical insurance;
- Patient history: T2DM, hypertension, hyperlipidemia, coronary heart disease, atrial fibrillation, heart failure, stroke (ischemic and hemorrhagic), transient ischemic attack (TIA), cataracts, and macular degeneration;
- History of surgical intervention: coronary intervention, coronary artery bypass grafting and coronary angiographic stenosis;
- Questionnaire: Edinburgh Intermittent Claudication Questionnaire (ECQ) ;
- Physical examination: blood pressure, heart rate, height and weight;
- Clinical assessment information: blood glucose (including HbA1c , fasting blood glucose,

two-hour postprandial blood glucose), renal function (including serum creatinine glomerular filtration rate, UACR), blood lipids (including total cholesterol, LDL cholesterol, HDL Cholesterol, triglycerides), funduscopy, and the detection frequency of the above inspections in the past year (mainly based on patient self-report);

- Whether the doctor prescribes urine routine examination for inpatients, and whether the doctor issues a new doctor's order after the outpatients report back the renal function examination;
- Combined drug information: this prescription drug and commonly used drugs (outpatients) and medications during hospitalization (inpatients);
- Information about patient behavior: smoking history and drinking history;
- UACR value detected on the day of enrollment;
- The result of funduscopy gained on the day of enrollment.

4.2 Definition of diseases involved in the research

1) Hypertension is defined as: When blood pressure was measured on different days without antihypertensive drugs, patients had systolic blood pressure ⩾140mmHg and/or diastolic blood pressure ⩾90mmHg; Or patients with a history of hypertension who are currently taking antihypertensive medications and whose blood pressure is less than 140/90 MMHG are also diagnosed with hypertension. (For patients with newly diagnosed hypertension, it is recommended to return to the clinic and register after diagnosis. If there is no follow-up after the initial visit, registration will not be granted).

2) Diabetes is defined as: There are diabetes symptoms such as polydipsia, polyuria, polyphagia, and weight loss plus random blood glucose ⩾ 11.1mmol/L.. Fasting blood

glucose is ⩾7.0mmol/L; blood glucose is ⩾11.1mmol/L in 2 hours oral glucose tolerance test. Patient with a history of diabetes and is currently using hypoglycemic drugs should be considered diabetes even their blood sugar is normal.

3) Hyperlipidemia is defined as: In the absence of lipid-lowering drugs, for fasting measurement of blood lipids, total cholesterol is ⩾6.2mmol/L or low-density lipoprotein is ⩾4.1mmol/L or triglyceride is ⩾2.3mmol/L. Patient with a history of hyperlipidemia and is currently using lipid lowering drugs should be considered hyperlipidemia even their blood lipid is at a normal level

4) Coronary heart disease is defined as: Any history of myocardial infarction, coronary artery bypass grafting, coronary intervention, or coronary artery stenosis >50%, or typical angina symptoms, and evidence of myocardial ischemia on electrocardiogram or echocardiography segmental wall motion abnormalities.

5) Heart failure is defined as: typical symptoms and signs of heart failure such as nocturnal paroxysmal dyspnea, reduced exercise tolerance, bilateral ankle joint edema, and left ventricular ejection fraction <40%; or there are typical symptoms and signs of heart failure, left ventricular ejection fraction ⩾ 40%, elevated BNP, left ventricular hypertrophy/left atrial enlargement or abnormal ventricular diastolic function; or a history of heart failure in the past, currently taking heart failure-related drugs, although there are no symptoms and signs of heart failure and laboratory findings, still diagnosed as heart failure.

6) Atrial fibrillation is defined as: single-lead electrocardiogram (⩾30 s) or 12-lead electrocardiogram (⩾10s) shows that P wave disappears and is replaced by fibrillation

wave (f wave) with irregular size, shape and duration, the RR interval is absolutely irregular; or there is a history of atrial fibrillation in the past, and the drug related to atrial fibrillation is currently being taken. Although the electrocardiogram does not show the performance of atrial fibrillation, it is still diagnosed as atrial fibrillation.

7) Severe infection is defined as: life-threatening infection, including systemic inflammatory response syndrome, sepsis, septic shock or systemic multiple organ dysfunction syndrome.

8) Primary glomerular disease is defined as: a disease of unknown etiology, often involving bilateral glomeruli, with hematuria, proteinuria, edema, hypertension, renal dysfunction, etc. as the main clinical manifestations, including acute glomerulonephritis, rapidly progressive glomerulonephritis, chronic glomerulonephritis, asymptomatic hematuria and/or proteinuria, and nephrotic syndrome.

9) CSS score of cachexia is defined as: patients with CSS ⩾ 5 points are considered to be in the state of cachexia, refered to the "2020 Guidelines for the Clinical Diagnosis and Treatment of Cancer Cachexia", adopted the CSS Cachexia Staging Scale .

4.3 Research procedure

The patient recruitment consisted of two parts, 50 patients from outpatients attending the Department of Cardiology and 50 from in patients receiving treatment in the Department of Cardiology.

- In the outpatient department, a selected, representative cardiologist should be followed and eligible patients among the physician's visits would be continuously screened. It is necessary to communicate with the person in charge of the Department of Cardiology

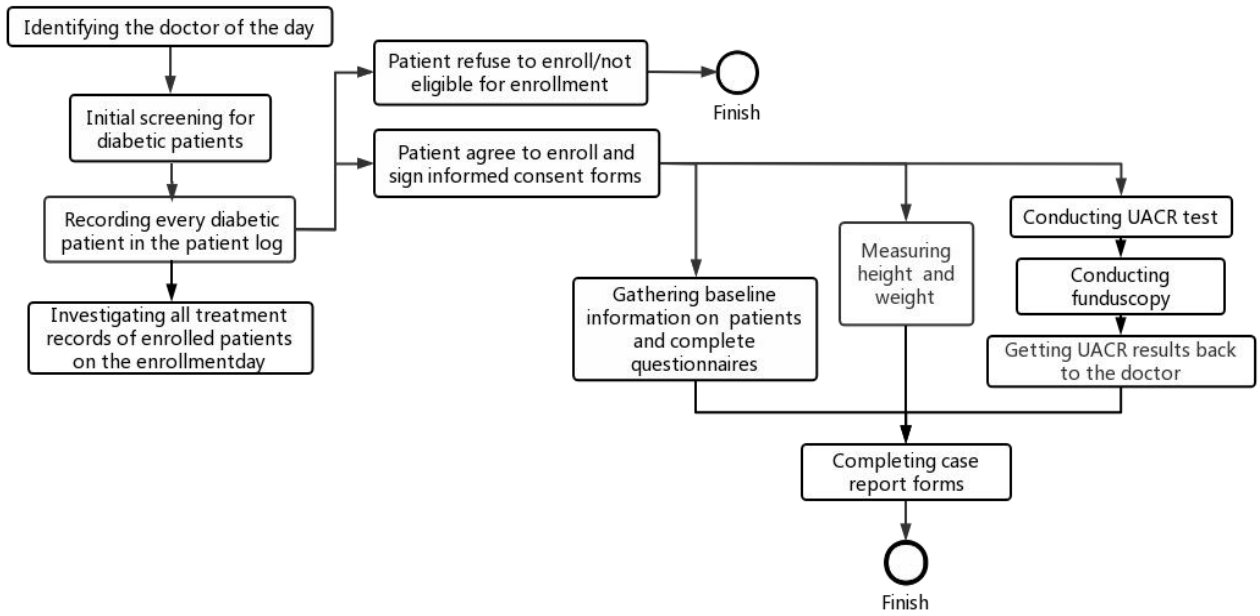
before the start of the branch center to determine the following outpatient doctors, and plan and determine the enrollment process with the outpatient doctors in advance. On the screening day, record and follow the T2DM patients encountered by the doctor during the consultation process, communicate with the patient for informed consent, screen according to the inclusion criteria, and generate a study number for those who meet the enrollment criteria (see flow chart 1).

- In the ward selected by the inpatient department of the Department of Cardiology, the clinical coordinator conducts a preliminary examination of all inpatients in the ward through the hospital medical record system, records the patient with T2DM, and communicates with the patient for informed consent, according to the inclusion and exclusion criteria, screening is carried out, and those who meet the inclusion conditions are enrolled and a research number is generated (see flow chart 2).

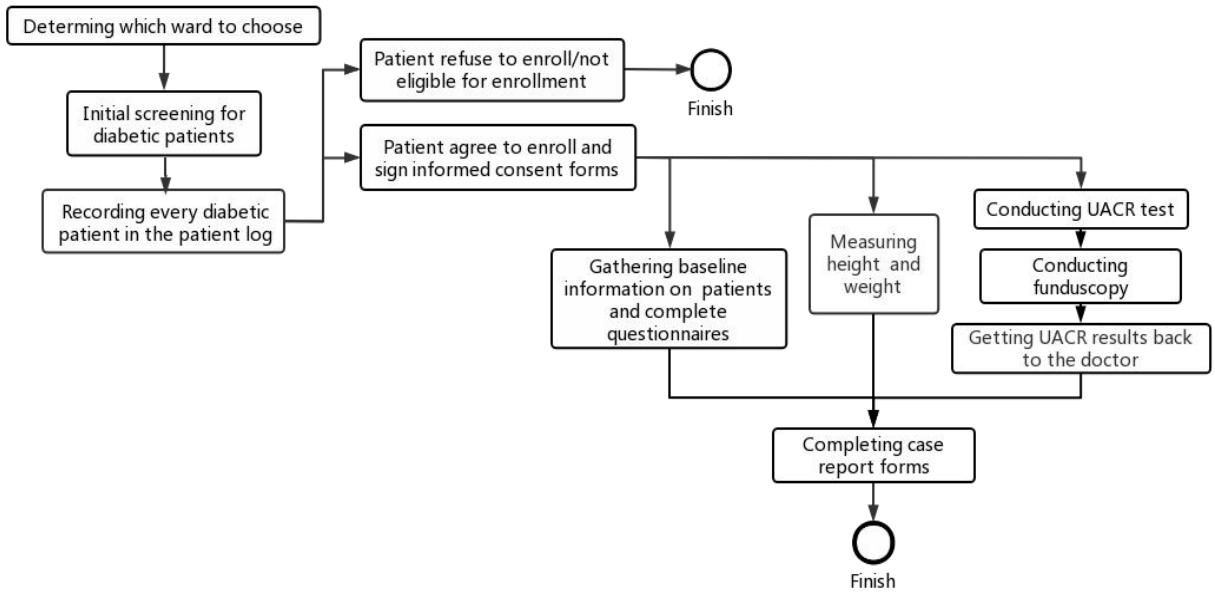
A face-to-face questionnaire should be conducted on the enrolled patients and baseline information such as, medical history, clinical assessment information, medication information, and living habits should be collected; and physical examination, UACR tests and funduscopy were performed on the patients. For outpatients, it is also necessary to query all the medical records of the enrolled patients on the day after the day of enrollment to supplement any missing information.

To evaluate the doctor's attention to chronic kidney disease, this study mainly reviewed the doctor's order to observe whether the doctor prescribes the UACR checklist for patients with T2DM to monitor the renal function of the patients. If the doctor has issued a UACR test for the patient, record the inspection value; if the doctor has not prescribed the test, use the

UACR measurement equipment provided in this study to obtain the results. When all the research-related information of the enrolled patients is collected, and the UACR results are obtained and fed back to the doctors, the data collection process is deemed to be over. In addition, after the doctor obtains the results of the UACR examination, whether to revise the doctor's order based on the detected nephropathy is also one of the ways to measure the doctor's awareness of the identification and management of the nephropathy of diabetic patients in the cardiology department.



Flowchart 1, Outpatient enrollment process



Flowchart 2, Inpatient enrollment process

5 Research evaluation

5.1 Clinical evaluation

During the study period, the clinical data and demographic data of the enrolled patients will be measured and recorded, including gender, age, height, weight, as well as disease history, drug history, smoking status, and drinking status. The physical examination will also collect basic physiological data such as blood pressure and heart rate to assess the patient's basic physical characteristics.

5.2 Medical record inquiry

The indicators examined will be retraced by querying the HIS electronic medical record system. The medical records will be queried for the most recent transcripts of relevant tests such as blood glucose, lipids, blood tests and renal function of the enrolled patients in the last three months, to check for logical matches of disease or medication history, and combined with the patient's self-reported record of the frequency with which he/she has

monitored and managed the indicators in the past year.

5.3 Laboratory inspection

During the study period, dry urine cups will be taken and fresh randomized mid stage urine samples will be collected from patients in the study group. Portable urine testing instruments (such as the Mission ACON U120 Ultra/EMPSUN Enpusen urine testing machine and 14 test strips, which are purchased by the sponsor and provided to each center, are used to measure the patient's microalbumin and urine creatinine data by using dry chemical methods, namely test strips, see appendix 2). And the UACR value will be calculated by using the formula UACR(mg/g)=urine microalbumin(mg/L)*1000/(urine creatinine(mmol/L) * 0.113).

During the study period, portable fundus cameras (which are purchased by the sponsor and provided to each center, with equipment examples shown in appendix 3) will be used to take fundus photos of enrolled patients, and the results obtained immediately will be fed back to the doctors and patients.

5.4 Physician behavior and kidney disease management

After collecting the urine sample and calculating the UACR value, the patient will feed back the test results to his/her doctor. This study will record the doctor's current diagnosis, and use the method of reviewing medical records to evaluate whether he/she provides a new diagnosis and prescription for the patient's renal function.

6 Statistical Considerations

6.1 General considerations

This study will be performed using SAS 9.4 statistical software. Descriptive statistics are calculated and reported, including number of observations, means, standard deviations, medians, and interquartile ranges for continuous variables, and frequencies and percentages for categorical variables. Percentages will be calculated based on non-missing data unless otherwise specified. The data will be checked for bias and outliers. Conversion will be done as needed. Missing data will be assumed to be missing at random or completely at random, and no imputation will be applied except in special circumstances.

6.2 Definition of analysis set

The full analysis set will include all enrolled participants with UACR data.

6.3 Outcome Analysis

6.3.1 Main endpoint

The primary endpoint of this study will be the prevalence of albuminuria (UACR ⩾ 30 mg/g) in patients with type 2 diabetes presented to the Department of Cardiology , and the prevalence of albuminuria and other demographic characteristics will be assessed by descriptive abstracts. In summary, the relationship between the stage of renal impairment/disease (A1-A3 or GFR classification) and relevant covariates was analyzed by logistic regression model. Crude ORs and multivariate-adjusted ORs will be reported, including covariates including:

Age group (18-39 years old, 40-59 years old, 60-69 years old, ⩾70 years old); gender; BMI group (18.5, 23.9, 27.9, 28), blood pressure, blood lipid (LDL, HDL, TG), living habits (smoking, drinking); sub-research centers, nephrotoxic drugs being used, disease history.

Prevalence will be analyzed grouped by stratification factors, gender and age, geographic

region (East, South, Central, North, Northwest and Southwest), etc.

6.4.2 Secondary endpoints

(1) Albuminuria level in patients with T2DM in the Department of Cardiology (microalbuminuria means UACR value >30 and <300 mg/g; macroalbuminuria means UACR value ⩾ 300 mg/g);

(2) The prevalence and level of albuminuria in different types of cardiovascular diseases in the Department of Cardiovascular Medicine (microalbuminuria refers to UACR values >30 and <300 mg/g ; macroalbuminuria refers to UACR values ⩾300 mg/g);

(3) Different treatment patterns for patients with CKD and patients without CKD;

(4) Assessing the current status of disease-related risk factor management in patients with T2DM attending cardiovascular medicine departments at different levels of hospitals;

(5) Evaluating the management of complications in patients with T2DM in different levels of hospitals.

6.4.3 Exploratory endpoint

The prevalence of retinopathy in patients with T2DM and the level of retinopathy in patients with T2DM in the Department of Cardiology.

6.5 Bias and confounding factors management

6.5.1 Bias

The research hospital of this study selects representative medical centers of different grades distributed in six geographical regions of China. The research population chooses a continuous population of diabetic patients in the Department of Cardiology, including outpatients and inpatients, to reflect the real situation of cardiovascular patients with type 2

diabetes, which reduces the selection bias to a certain extent. The data collection of this study adopts the combination of participants' self-report and retrospective of the case system to ensure the accuracy of the collected survey data and reduce the information bias to a certain extent.

6.5.2 Confounding

The data analysis of this study will stratify the center, gender, age, concomitant medication and other factors, and control and correct the influence of potential confounding factors on the results through multivariate regression analysis. Model assumptions will be checked and, if necessary, appropriate transformations or nonparametric analysis methods will be used.

6.6 Sample size estimation

According to studies published in 2007[28] and 2005[29], among hypertensive patients with T2DM, the detection rate of albuminuria in 2,473 patients in mainland China was 59.9%, and the detection rate of albuminuria in 5,549 patients in 6 countries in Asia was 58.6%.

There were no pre-defined statistical hypothesis tests and power analyzes for this study. Based on the enrollment of 30 participating units in two different levels (18 in the tertiary level and 12 in the secondary level), assuming a prevalence rate of 50% and a target sample size of 3,000 patients. Therefore, at least 100 cases were selected for each participating unit, which can provide an accuracy of 3.6%, and the 95% CI is 48.2%, 51.8%.

Total number of analysis	Prevalence	Number of related	9 5% confidence interval	9 5% confidence interval width (%)

sets		events		
1,000	50 %	500	46.9% , 53.2%	6.3%
1,500	50 %	750	47.4% , 5 2.6%	5.2 %
2,000	50 %	1,000	47.8% , 5 2.2%	4.4%
3,000	50 %	1,500	48.2% , 5 1.8%	3.6 %
5,000	50 %	2,500	48.6 %, 51.4%	2.8%
9,000	50 %	4,500	49.0 % , 51.0 %	2.0 %

7 Research and Data Management

7.1 Data collection and management

7.1.1 Confidentiality

The research documents will be properly kept, and the paper originals will be kept by the local research center according to regulations. Electronic files and data will be stored in a non-URL-accessible area, and it is only accessible through the website, and only authorized researchers who have completed training in data handling will have access to the data. Access to the database is controlled by setting the user ID and password system. All passwords stored in the system will be encrypted using SSL .

7.1.2 Anonymization, de-identification and destruction

Each enrolled patient will be assigned a unique identification code. Any medical records or data sets transmitted to the sponsor will only represent the patient with this code, with any personally identifiable information anonymized. All laboratory reports uploaded to the database according to the regulations must be deprived of privacy before uploading, and

identifiable personal information can be covered before uploading to ensure patient privacy. Biological samples generated during the research will be destroyed immediately after analysis.

7.1.3 Source data

The source data will include original medical records, patient screening forms, instrument inspection reports, questionnaires and case report forms for filling in the data collection site, and all other documents used to record patients' diagnoses and treatment in the hospital. The research center should provide past medical records, including patient medical history, surgical history, and access to various examinations and diagnoses.

7.2 data management

Recording and reporting study data is via paper or electronic case report form (CRF). The researcher needs to sign the paper CRF. Researchers must be responsible for preserving and providing accurate source data. Researchers must allow research-related monitoring, auditing, ethical review, and regulatory agency inspections, and provide source data or documents for their inquiries. The sponsor or designee is responsible for data management of this study, including data quality checks. Unless local regulations or institutional policy require a longer retention period, investigators must ensure that records and documents related to this study (including signed informed consent forms) are retained for 10 years after completion of the study. No records shall be destroyed during the retention period without the written approval of the sponsor. No records shall be transferred to another location or to a third party without written notice to the sponsor.

7.3 Quality control

The researcher must electronically signed CRF before submission. Any obvious errors or omissions in the data or forms that need to be clarified require further inquiries and verification directly with the medical center from which the data originated. Additionally, key data may be double-keyed for additional quality control. During the study period (screening, initiation, enrollment, and end), the sponsor will send monitors to conduct at least one monitoring at each participating research center. The sponsor will organize audits as needed.

8 Regulatory, Ethics and Research Oversight

8.1 Safety and Adverse Events

Although the likelihood of safety issues or adverse events arising from the implementation of this study is small, unexpected conditions (including serious adverse events and adverse events) that may be directly related to the study will be continuously monitored and reported as required. AEs that meet timely reporting requirements will be summarized in a narrative or other form and submitted to the IRB at follow-up review (if there is a follow-up review), or will be recorded and followed up on the patient case report form but not submitted to the IRB (if no follow-up review is required).

8.2 Ethical review and protocol changes

IRB/IEC review and approval were required before initiation. During the research period, if there is any modification to the research documents such as the research protocol and informed consent form, it needs to be reviewed, approved or filed again by the IRB/IEC (according to the specific requirements of the IRB /IEC). During the research period, a

written summary of the research progress shall be provided to the IRB/IEC as required, and the IRB/IEC and other applicable regulations shall be complied with.

The researcher/institution agrees to allow the auditor or monitor to have direct access to all relevant documents, and to arrange time to cooperate with the auditor/monitor to discuss issues and any issues found. Audits and monitoring can be done at any time during or after the study.

8.3 Informed consent procedure

Since no intervention is involved, potential participants will be informed quickly through electronic or paper informed consent, and researchers at each center must explain the following in detail to patients:

- Voluntary participation and the right to withdraw from the study at any time at any stage, without discrimination or retaliation, without affecting the patient's medical care and rights.
- Participation in research and personal data are confidential.
- According to the Declaration of Helsinki, patients should be informed of the nature, purpose, possible expected benefits and risks of the research. Ensure that patients have enough time to consider whether they are willing to participate, and sign the informed consent.
- One original copy of the signed informed consent form was handed over to the patient, and the other original copy was properly kept in the local center.

8.4 Data protection

Investigators must inform participants about how their personal study-related data or medical records will be used, and they must explain to them the extent of disclosure and

that their medical records may be reviewed by authorized personnel designated by the sponsor or by IRB/IEC and regulatory authorities.

8.5 Study Discontinuation

Participants may request to withdraw informed consent and withdraw from the study at any time. The study did not involve an intervention, and adverse events will not be discontinued or the center closed, but adverse events will be recorded in the study file. The sponsor, investigator, or regulatory agency may decide to suspend the study, or part of it, for safety or administrative reasons after reaching an agreement.

Appendix 1

Patient Screening Form

Screening Date	Serial Number	Medical Record Number	Name	Age	Gender	Enrollment Success	Reasons for Enrollment Failure	ID
					☐Male ☐Female	☐Yes ☐No	☐Patient Refused Enrollment ☐Patient Does Not Meet Inclusion Criteria	

Appendix 2

Comparison chart of UACR tester and 14 test papers

Appendix 3

Portable fundus camera

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