



STUDY PROTOCOL

A 24-Week, Multi-Center, Randomized, Open-Label Clinical Trial Comparing the Effects of Xuezhikang and Atorvastatin on Glucose Metabolism in Patients with Dyslipidemia and Prediabetes (XTREME Study): Design of the Study Protocol

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Abstract

Background: Statins, a first-line therapeutic option for atherosclerotic cardiovascular disease (ASCVD), have prompted concerns regarding dysglycemia and diabetes, thus posing a dilemma in treating patients with prediabetes. Xuezhikang (XZK) decreases blood cholesterol levels without affecting glucose metabolism, and may serve as a potential substitute.

Methods: The XTREME study is a prospective, randomized, open-label, multi-center trial evaluating whether XZK 1200 mg/d, compared with atorvastatin 20 mg/d, has favorable effects on HbA1c levels after 24 weeks of treatment in patients with dyslipidemia and prediabetes. After a 1-week run-in period for adherence assessment, the study will randomly assign (1:1) 392 patients meeting the protocol inclusion criteria to one of two treatment groups: an experimental group (XZK 1200 mg/day) or a control group (atorvastatin 20 mg/day). All participants will be recruited from approximately 20 Chinese medical centers. The last participant is planned to be recruited before December 2023. The primary endpoint will be change in HbA1c level from baseline to 24 weeks, or before anti-diabetic therapy initiation within 24 weeks. The key secondary outcomes will include other biomarkers reflecting blood glucose or lipid metabolism.

Discussion: Delaying diabetes is desirable for individuals with prediabetes. The XTREME trial presents a unique opportunity to demonstrate whether XZK might provide an alternative to statins for patients with dyslipidemia and prediabetes.

Keywords: Xuezhikang; Type 2 diabetes mellitus; Atorvastatin

Trial registry: ChiCTR, ChiCTR2200056381 registered February 4, 2022 <https://www.chictr.org.cn/showproj.html?proj=142619>

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Introduction

Background and Rationale {6a}

In clinical practice, statins should be the first line therapeutic option for atherosclerotic cardiovascular disease (ASCVD). According to the 2016 Chinese guidelines for the management of dyslipidemia in adults, Xuezhikang (XZK) 1200 mg/d, atorvastatin 20 mg/d, and other statins are recommended as first-line therapies for cholesterol control. [1, 2] However, statin-treated individuals have an elevated risk of dysglycemia and incident type 2 diabetes mellitus (T2DM) [3–5]. The long-term administration of statins might increase the risk of new-onset diabetes by approximately 9% [6]. Recent findings from systematic evaluations of observational studies have linked statin use to a modest rise in HbA1c in patients with T2DM: the mean HbA1c was 0.17% (95% CI 0.07, 0.27) higher in patients taking statins than in those not taking statins [2, 7]. Consequently, managing patients with dyslipidemia in prediabetes with statins to lower blood cholesterol levels comes at the cost of higher risk of dysglycemia and T2DM [8].

XZK is a red yeast rice purified preparation containing a family of naturally occurring statins, including monacolin K, which is equivalent to lovastatin (Mevacor) in lipid-lowering therapy [9]. A meta-analysis has indicated significantly lower LDL-C with XZK therapy than control treatment [10]. Additionally, a retrospective cohort study using Taiwan's National Health Insurance data for 34,504 individuals receiving red yeast rice prescriptions from 2010 to 2014 has revealed a lower risk of incident diabetes in that cohort than in a lovastatin cohort (HR:0.46, 95% CI 0.43–0.50) [11]. A variety of mechanisms may underlie the lower diabetes incidence in the patients receiving XZK. N-3 polyunsaturated fatty acids are a primary component of XZK that influences the activity of critical transcription factors regulating gene expression involved in lipid metabolism and enhances insulin sensitivity in patients with T2DM, thereby preventing diabetic complications. A 6-week n-3 polyunsaturated fatty acid supplementation regimen has been found to increase postprandial microvascular performance while decreasing the postprandial decline in macrovascular function [12]. Moreover, XZK has shown a positive safety profile as a post-market medication.

After extensive clinical use, the most common adverse effects have been found to be minor gastrointestinal symptoms [13–15].

Choice of Comparators {6b}

Atorvastatin 20 mg is a moderate intensity statin widely used in clinical practice. A cohort study based on a Korean population database has reported that the use of low dose atorvastatin 10–20 mg tends to be a risk factor for new-onset diabetes in Asians [16]. Meanwhile, a small RCT has reported an increase in HbA1c levels from 6.1% to 6.5% after atorvastatin 20 mg/d treatment for 2 months [17].

Study Objective {7}

This study is aimed at determining whether XZK 1200 mg/d, compared with atorvastatin 20 mg/d, has favorable effects on HbA1c levels from baseline to 24 weeks in patients with dyslipidemia and prediabetes.

Trial Design {8}

The XTREME study is a prospective, randomized, open-label, multi-center trial with a sample size of 392 participants. Participants meeting all inclusion criteria and no exclusion criteria will be randomly allocated in a 1:1 ratio to an XZK group or atorvastatin group, stratified by center and age (≥ 60 years old, < 60 years old). After providing signed informed consent, participants will be randomized within 7 days, and will receive the assigned intervention and undergo four follow-up over 24 weeks.

The flowchart for the trial procedure is shown in Figure 1.

Methods

Study Setting {9}

The study will be led by Beijing Anzhen Hospital, Capital Medical University, where a complete set of regulations for ethical review, informed consent, sample collection, participant protection, and human genetic resource management is applied. Recruitment will occur at approximately 20 centers, including public or private hospitals. Beijing

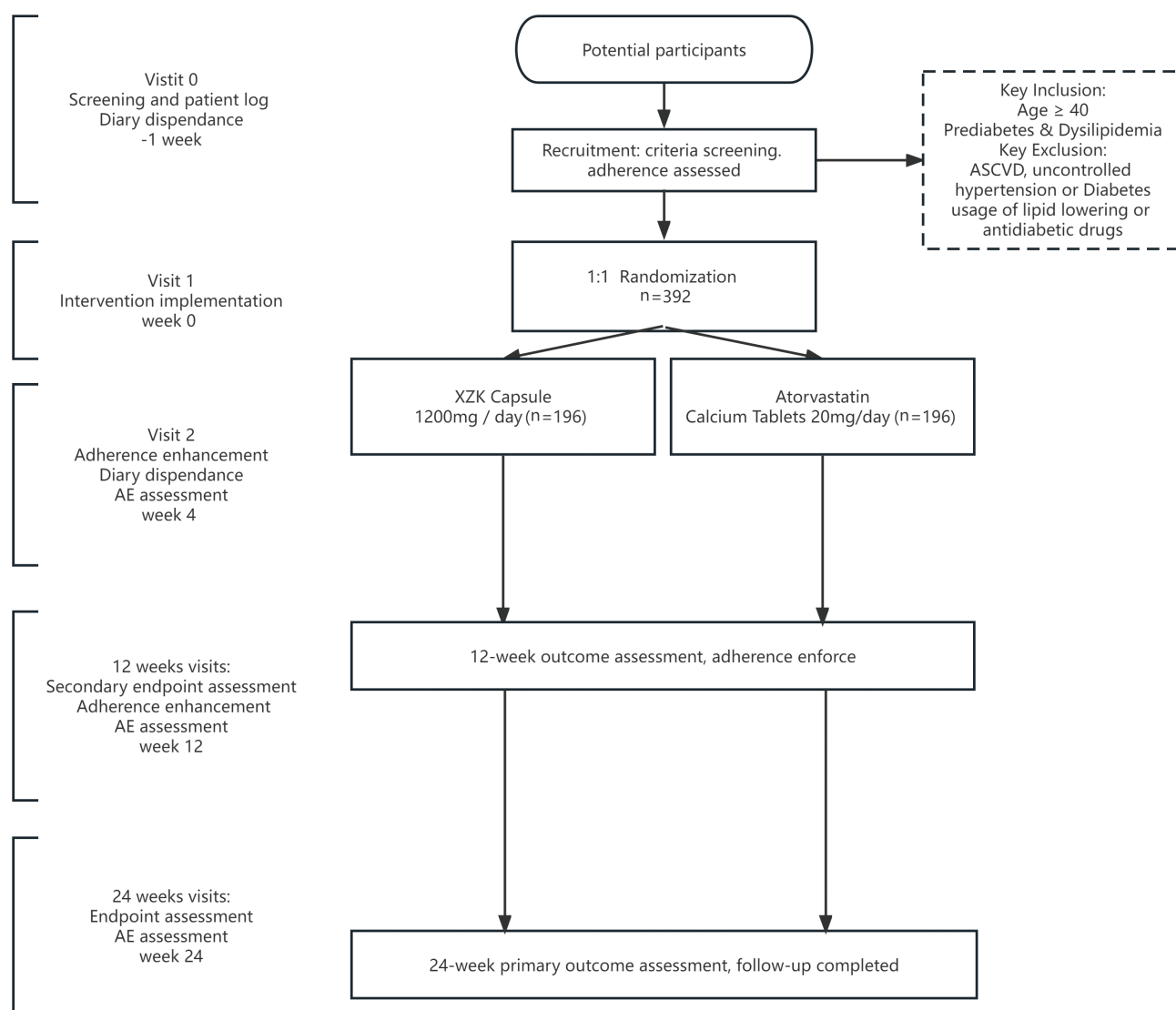


Figure 1 Trial Procedure.

Anzhen Hospital's medical team will evaluate the centers to ensure that a proper management system is in place, with necessary areas, staff, and participant populations for the trial.

The planned milestones for the trial's overall timeline are as follows:

First participant inclusion: July 2022

Last participant inclusion: December 2023

Last participant last visit: June 2024

Clinical study report: December 2024

Eligibility Criteria {10}

Inclusion Criteria

- (1) Written informed consent provided
- (2) Age ≥ 40 years

- (3) Diagnosed prediabetes, meeting one of the following conditions:

✓ Impaired fasting glucose: $5.6 \text{ mmol/L} \leq \text{FPG} < 7.0 \text{ mmol/L}$

✓ HbA1c $5.7\text{--}6.4\%$ ($39\text{--}47 \text{ mmol/mol}$)

- (4) Dyslipidemia, meeting one of the following conditions:

✓ Fasting LDL-C $\geq 3.4 \text{ mmol/L}$ and $< 4.9 \text{ mmol/L}$, and TG $\leq 5.6 \text{ mmol/L}$

✓ Fasting non-HDL-C $\geq 4.1 \text{ mmol/L}$ and $< 5.7 \text{ mmol/L}$, and TG $\leq 5.6 \text{ mmol/L}$

Exclusion Criteria

- (1) Demonstrated or documented ASCVD, including acute coronary syndrome, history

- of myocardial infarction, stable or unstable angina pectoris, coronary or other revascularization, ischemic stroke, transient ischemic attack, peripheral vascular disease, etc.
- (2) Diagnosed diabetes, according to the 2021 American Diabetes Association “Standards of Medical Care in Diabetes,” meeting one of the following conditions:
 - ✓ FPG ≥ 126 mg/dL (7.0 mmol/L)
 - ✓ Known 2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT
 - ✓ HbA1C $\geq 6.5\%$ (48 mmol/mol)
 - ✓ Random plasma glucose ≥ 200 mg/dL (11.1 mmol/L) In patients with classic symptoms of hyperglycemia or hyperglycemic crisis
 - (3) Use of any lipid lowering drugs in the prior 3 months, including but not limited to statins, bile acid sequestrants, cholesterol absorption inhibitors, PCSK9 inhibitors, nicotinic acid, fibric acid derivatives, fibrates, other traditional Chinese medicines, and n-3 fatty acids
 - (4) Use of any antidiabetic drugs
 - (5) Contraindications to XZK or atorvastatin:
 - ✓ Allergy to XZK or atorvastatin
 - ✓ Pregnancy or breastfeeding
 - (6) Uncontrolled hypertension (systolic blood pressure ≥ 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg) at screening
 - (7) Active liver disease or hepatic dysfunction, including continually elevated liver transaminase due to unknown causes; abnormal liver function test at baseline (ALT or AST $> 3\times$ the ULN)
 - (8) Known renal dysfunction or elevated serum creatinine levels at baseline (with eGFR ≤ 60 mL/min/1.73 m²)
 - (9) Other endocrine diseases that might influence lipid or lipoprotein levels, such as hypothyroidism
 - (10) Participation in clinical trials for other drugs in the prior 3 months
 - (11) Previous statin treatment causing an increase in creatine kinase (CK) by $10\times$ the ULN, or myalgia myopathy (muscle pain or muscle weakness, accompanied by CK exceeding $10\times$ the ULN)
 - (12) Estimated life expectancy < 6 months at the time of enrollment
 - (13) Excessive use, or a history of excessive use, of alcohol

- (14) Close affiliation with the investigators, e.g., a close relative or dependent person (e.g., employee or student relationship)

Intervention Description {11a}

Intervention group: XZK capsule, 1200 mg/day, in two capsules twice per day, taken after meals in the morning and evening. Continuous treatment for 24 weeks. The study agent is produced by WBL Peking University Biotech Co.

Control group: atorvastatin, one tablet once per day, before bedtime. Continuous treatment for 24 weeks. The study agent is produced by Pfizer Inc.

Criteria for Discontinuing or Modifying Allocated Interventions {11b}

Criteria for discontinuation from trial treatment include the following:

- 1) Meeting the criteria for possible drug-induced liver injury
 - ALT or AST $> 8\times$ the ULN
 - ALT or AST $> 5\times$ the ULN for more than 2 weeks
 - ALT or AST $> 3\times$ the ULN and (TBL $> 2\times$ the ULN or INR > 1.5)
 - ALT or AST $> 3\times$ the ULN, with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$)
- 2) Diagnosis of rhabdomyolysis
- 3) Pregnancy
- 4) Investigator considering that the study drug is harmful to the safety or health of the participant
- 5) Participant requesting to stop taking the test drug
- 6) Sponsor requiring participants to permanently stop taking the study drug

Individuals who permanently stop taking the study medication will be followed, and outcome events and vital status will still be recorded until the scheduled study end date. Patients should not be re-exposed after stopping the study medication.

Strategies to Monitor and Improve Adherence to Interventions {11c}

Patient adherence will be assessed during a 1-week run-in period. To be considered to have good

compliance and to be recruited into the trial, patients must complete more than five daily patient logs during the screening period. Throughout each visit, adherence to the study drug will also be assessed and reinforced. The study medicine will be self-administered by participants in both arms at home, and compliance with the research intervention will be evaluated at each visit. Moreover, adherence will be monitored by counting the returned tablets and examining patient logs during the site visits.

Concomitant Care {11d}

Any drugs or combination treatments that might affect sugar metabolism, such as metformin and steroids, will be prohibited. In addition to the drugs listed above, other drugs will be permitted to be used in combination therapy, if considered necessary by the investigators. Any treatment received by patients during the study will be recorded in the CRF. If a study drug is stopped because of adverse effects, every attempt will be made to restart the treatment, whenever possible. Generally, rechallenge of participants with substantial AT elevations ($>5\times$ the ULN) should not be attempted.

Outcome {12}

The XTREME study anticipates observing alterations in blood lipids and elevation in blood sugar or insulin resistance after 6-week and 8-week intervention periods [18–21], respectively, and stabilization of both parameters after 24 weeks of intervention [22, 23]. Furthermore, newly diagnosed diabetes or glucose-lowering therapy requirements during the follow-up period are anticipated, thus potentially affecting blood glucose levels or other biomarkers at the end of the 24-week period [24]. Therefore, the primary endpoint of this study will be the change in HbA1c levels from baseline to 24 weeks, or before antidiabetic therapy initiation within 24 weeks.

The key secondary endpoint will focus on the change in HbA1c levels after 12 weeks, followed by changes in FBG, PPG 2 h, and HOMA-IR from baseline to both the 12-week and 24-week timepoints. Moreover, the percentage change in LDL-C and non-HDL-C levels between baseline and both the 12-week and 24-week intervals will be analyzed.

Adverse events, abnormal physical examination findings, and abnormal laboratory data (ALT, CK, etc.) will be monitored, but no comparison between arms will be performed.

Participant Timeline {13}

See Appendix 3, Table 1 for the schedule of activities.

Sample Size {14}

The primary endpoint of the study is the change in HbA1c levels from baseline to 24 weeks or before antidiabetic therapy initiation within 24 weeks. We expect that the HbA1c level will not change in the XZK group, and an 0.3% increase in HbA1c level will be observed in the atorvastatin 20 mg group, on the basis of findings from previous research [16, 17, 24]. The expected SD of the change in HbA1c level is 1.0% for both treatments. The sample size of each group of 176 participants will provide 80% power to detect an 0.3% HbA1c difference at a 5% significance level. To account for a 10% dropout rate, the target sample size will be 392.

Recruitment {15}

Patients meeting the admission criteria will be selected through each hospital's physical examination center. The electronic medical records will be verified to screen suitable patients. Additional important recruitment strategies will be center advertising, including social media, and promotion by physicians. Patients will be provided with small incentives to enroll, such as free medicine, a free medical examination, reimbursement of transportation costs for follow-up visits, etc.

Assignment of Interventions: Allocation

Sequence Generation, Concealment Mechanism, and Implementation {16a,b,c}

Participants will be randomized with the Interactive Web Response System (IWRS), an online central randomization service. Allocation concealment will be ensured, because the service will not release the randomization code until the patient has been recruited into the trial.

Randomization will be requested by the investigator. In return, IWRS will send an answer form to an investigator not involved in assessing the outcomes of the study. The investigator will then give the treatment allocation information to the patient. Staff responsible for outcome adjudication will not be allowed to receive information about patient allocation.

Assignment of Interventions: Blinding {17a,b}

XTREME will be an open-label study: patients will be aware of their treatment. However, the statistical analysis will be conducted by blinded analysts unaware of treatment allocation.

Methods: Data Collection, Management, and Analysis

Data Collection Plan {18a}

The Participant Tracking System is a fully integrated tracking and notification system that will be used by clinicians to recommend participant follow-up windows and organize laboratory work throughout the study. As patients are recruited, the system will automatically prepare a monitoring schedule from the screening phase. The recommended follow-up window will be generated and delivered to the data accessor when the patient is enrolled in the trial. Data accessors on site will also be educated to ensure proper follow-up. To increase data reliability, an experienced contract research organization team will monitor and assist with data collection.

Data Collection Plan: Retention {18b}

Loss to follow-up will be defined as incomplete ascertainment of the primary outcome for trial participants who were randomized. If a participant does not return to the clinic for a required study visit, the site must make every effort to regain contact with the participant and reschedule the missed visit as soon as possible. These attempts at contact will be recorded in each participant's medical record. No records of randomized participants may be destroyed without the written approval of the sponsor.

Data Management: Process to Promote Data Quality {19}

The clinical coordinator will ensure the accuracy and completeness of the entry of participant follow-up visit forms, including laboratory reports and any hospital records. During data entry, the clinical coordination center will periodically perform conformance checks and programming edit checks on key variables and tables from the sub-center data. When a check reveals missing data or inconsistency, the data will be flagged for further review. Simultaneously, the clinical coordination center will generate data editing reports for clinical centers and research committees, including data collection at each clinical center and highlighting missing items to inform sub-centers to make corrections. Copies of paper or electronic documents for study participants, including appropriate medical records, will be retained at the clinical site. These records will be kept in locked filing cabinets and/or filing rooms within secure office spaces.

Statistics: Outcomes {20a}

The primary endpoints will be analyzed with the covariance (ANCOVA) model with the treatment group (XZK, atorvastatin) as the group and baseline HbA1c as the covariate. The results will be presented as least squares means with 95% confidence intervals and P-values. Model assumptions will be explored and, if necessary, appropriate transformation or non-parametric analysis techniques will be used. The primary analysis set for this analysis is the full analysis set (FAS). The FAS will include all randomized participants who had taken at least one dose of the trial drug and had no missing HbA1c values at week 24. For each secondary endpoint, an ANCOVA model similar to that described for the primary analysis above will be used.

Analyses will be performed in SAS statistical software. Descriptive statistics will be calculated, including n; means, standard deviations, medians, and interquartile ranges for continuous variables; and frequency counts and percentages for categorical variables. Percentages will be calculated on the basis of non-missing data unless otherwise specified. Data will be examined for skewness and outliers. Transformations will be performed as needed.

Statistics: Additional Analyses {20b}

Subgroup analysis will be performed among men vs. women; ages ≥ 60 vs. < 60 ; and BMI ≥ 28 kg/m² vs. BMI < 28 kg/m². For each subgroup analysis, an ANCOVA model similar to that described for the primary analysis above will be used, but with additional terms identifying subgroup membership and the intervention by subgroup interaction. We will report the Hommel adjusted P-values for the interaction effects.

Safety Endpoints Analyses Adverse events will be coded according to standard terminology. The incidence of treatment-emergent adverse events (AE), serious AE (SAE), treatment-associated AEs, and AEs leading to discontinuation will be tabulated for each treatment group. Subgroup analyses of AEs will be conducted on the basis of stratification by factors such as sex. Comparisons between treatment groups for safety data will not be performed, because both arms use approved drugs.

Statistics: Analysis Population (ITT) and Missing Data {20c}

The study will analyze the participant data according to ITT principles. The FAS will be used for efficacy and safety analysis. The completer analysis set will include participants in the FAS who completed all study drug treatment and did not have missing HbA1c values at week 24. In all analysis sets, participant data will be analyzed according to ITT principles unless otherwise specified. Missing data will be assumed to be missing at random or completely at random. In general, imputation will not be applicable unless otherwise specified.

Oversight and monitoring

Charter and Responsibilities of the Data Monitoring Committee {5d}{21a}

The data monitoring committee will include clinical inspectors and a clinical research associate. Members of the data monitoring committee, under the leadership of the PI, will be trained in confidentiality regulations and data monitoring, and

will ensure that personal folders are established for each subject. Their main task will be to ensure that the experimental procedure is performed correctly in accordance with the protocol. This process will include ensuring the informed consent process for participants; discussing progress with clinical investigators to ensure that all protocol procedures and practices are being performed as required; and monitoring entry files to ensure that data are accurately and timely recorded in the CRF.

Interim Analysis {21b}

No interim analysis is planned.

Adverse Event Reporting and Harm {22}

The AE assessment will occur from the time of signing of the informed consent form through the entire course of the study. SAEs should be reported to the sponsor within 24 hours of their occurrence being detected by any research staff. If any SAE occurs in a patient taking XZK, the investigator or other site personnel should also inform the sponsor regarding whether a causal relationship with XZK is being considered.

Auditing {23}

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's quality assurance unit may arrange to conduct an audit to assess the study conduct at the study site and the study documents originating there. The investigator/institution will be informed of the audit outcome. Audits may occur at any time during or after completion of the study.

Ethics and Dissemination

Research Ethics Approval {24}

The protocol, protocol amendments, ICF, and other relevant documents (e.g., advertisements) must be submitted to an institutional review board (IRB) by the investigator, and reviewed and approved by the IRB before the study is initiated.

The investigator will be responsible for providing written summaries of the status of the study to the IRB in accordance with the requirements, policies, and procedures established by the IRB, and for notifying the IRB of SAEs or other significant safety findings, as required by IRB procedures. The investigator will also provide oversight of the conduct of the study at the site and adherence to IRB regulations.

Plans for Communicating Important Protocol Amendments to Relevant Parties {25}

If amendments to the study protocol are necessary, the revised or new version of the study protocol will be provided to or approved by the IRB. Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Consent or Assent {26a}

Written informed consent will be obtained by the site investigator or designee from each participant before any trial-specific activity is performed. The investigators at each center must explain the nature and purpose of the trial, and the predicted possible benefits and risks to each patient, as well as the different trial groups in which participants may be placed. Other treatment options and participants' rights and obligations will be in accordance with the declaration of Helsinki. Patients will have the right to withdraw from the trial at any time during any phase, and shall not be subject to discrimination or retaliation. Each participant will provide signed and dated informed consent before participating in the study. The original signed informed consent forms will be stored in the investigator's study file.

Confidentiality {27}

The confidentiality of all participant information will be protected at the clinical facility and the clinical coordination center. Participants will be assigned a unique identifier before enrollment. Participant records or data sets transmitted to the sponsor will contain only identifiers. Any information identifying participants will not be transferred.

Source images or forms containing personal information, such as informed consent forms, laboratory reports, etc., will be masked or replaced with identifiers at entry. Paper records and computer files will be safeguarded from unauthorized access.

Access to Data {29}

Because this is a multicenter experiment, the full analysis set will be available only to the lead researcher team. Primary investigators will only have access to the data sets for their sub-centers but not to the full analysis set. A password-protected file site will contain the cleansed data set, which will also not contain participant identification information, for confidentiality purposes. The cleansed data will be made available only upon reasonable request, with the primary investigator's approval.

Ancillary and Post-Trial Care {30}

The patients will be treated by the investigator according to the local guidelines. The choice of cholesterol modification medicine will be decided upon through shared decision-making between the investigator and the patient.

Researchers will educate participants in the implementation of supportive care, encompassing lifestyle modifications in terms of dietary adjustments, weight management, and physical activity. Participants will be instructed to adapt their diets according to appropriate caloric requirements and nutritional interventions for their existing conditions, including prediabetes.

Discussion

To date, no published RCTs have compared the effects of statins and XZK on glucose metabolism in people with prediabetes and dyslipidemia. Because of a lack of evidence, physicians face a dilemma in treating patients with dyslipidemia and prediabetes, given the adverse effects of statins on the risk of dysglycemia. Whether controlling cholesterol comes at the cost of increasing glycemia is unclear. For patients with prediabetes, delaying the onset of diabetes would be favorable. The XTREME study presents a unique opportunity to gather evidence of whether XZK might be a better treatment choice

than statins for patients with dyslipidemia and pre-diabetes, by considering both cholesterol metabolism and glucose metabolism.

Dyslipidemia and diabetes mellitus, the major risk factors for ASCVD, have prevalence values of 40.4% [1] and 10.9% [25], respectively, among Chinese adults. After controlling for age, gender, and BMI, Asians exhibit a 60% higher likelihood of developing diabetes compared to Europeans, potentially attributed to genetic susceptibility [10]. As the age of patients with diabetes has declined and the number of patients with prediabetes has increased in recent years, balancing the need for lipid lowering and the development of diabetes in Chinese and Asian populations is critical [26].

One strength of this study is its multicenter trial design, which enables enrollment of a wide range of patients and high representativeness. Dietary patterns, for example, are highly geographical, particularly in China, and are frequently overlooked as an important factor influencing blood glucose and lipid levels. Inclusion of multiple centers scattered across China could effectively mitigate the effects of dietary and other lifestyle differences. Overall, this aspect increases the representativeness of the experimental population and the generalizability of the results.

The use of a surrogate endpoint of HbA1c level over a short period (24 weeks) is one of the study's limitations, thus posing challenges in assessing the cumulative effects and overall benefits in preventing the development of glucose metabolism abnormalities and diabetes. Meanwhile, because of the potential non-compliance and inconsistencies in treatment administration, the study will instead include data from patients newly diagnosed with diabetes during the follow-up period before initiation of hypoglycemic therapy. However, given the expected infrequency of such cases, the influence of this effect will remain unclear until the experiment is completed. This study is planned to assess the influence of this effect on the endpoint through sensitivity analysis before construction of the analysis set. Another limitation arises from the lack of individual adjustments in intervention dosage for each patient. Although patients with elevated blood lipids who might require additional treatment and intensive lifestyle improvement will be carefully excluded to mitigate potential confounding factor, some degree of imbalance in background therapy may still be

introduced. Possible future research could involve conducting long-term trials with clinically significant endpoints, thereby affording opportunities to tailor interventions for individual participants and enhance the generalizability of the findings.

Trial Status

The current protocol version number is v6.0, updated February 7, 2023. The recruitment began in July 2022 and will be completed by approximately December 2023.

Declarations

Data Availability Statement

The raw data are not currently available. The results of this trial will be published and presented at scientific meetings. A results summary will also be posted to publicly available clinical trial registers, and a manuscript will be developed for publication in a peer-reviewed journal after the completion of the trial. Plans are in place to grant access to the full protocol, participant-level data and statistical code. The full protocol, datasets and statistical code will be available from the corresponding author upon reasonable request.

Ethics Statement

The study was approved by the Clinical Research Ethics Committee of Beijing Anzhen Hospital. Informed consent will be obtained from all participants and/or their legal guardians. All experiments will be performed in accordance with relevant guidelines and regulations (such as the Declaration of Helsinki).

Authors' Contributions

Lan Fu and Yiqun Zhang are the joint first authors and contributed equally to this manuscript. Xin Du is the corresponding author of this manuscript. Rong Han, Rong Hu, Craig S. Anderson, Linong Ji, and Changsheng Ma reviewed the manuscript.

The authors listed in the manuscript and subsequent articles will be in line with the authorship eligibility

guidelines. No professional writers or artificial intelligence will be used in drafting the articles.

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Conflict of Interest

The trial is funded by AstraZeneca, and the tested XZK is marketed exclusively by AstraZeneca.

Name and Contact Information for Trial Sponsor

The study is sponsored by the Ruyang Rural Health Institute (RRHI)

Address: Ruyang County People's Hospital, Ziluo hospital district, Henan, China

Role of Sponsor

On behalf of the sponsors, RRHI will perform regulatory control of the study. RRHI's responsibilities

will include pharmacovigilance, monitoring, building and managing clinical databases, enabling setup, and supervising protocol preparation and regulatory submission.

Planned Study Period

Date of enrollment of the first participant: July 2022

Estimated date of study completion for the last participant: April 2024

Supplementary Material

Supplementary material for this paper is available at the following links: Appendix 1 https://cvia-journal.org/wp-content/uploads/2024/01/Appendix_1._SPIRIT_2013_Checklist.pdf.

Appendix 2 https://cvia-journal.org/wp-content/uploads/2024/01/Appendix_2._Full_inclusion_and_exclusion_criteria.pdf.

Appendix 3 https://cvia-journal.org/wp-content/uploads/2024/01/Appendix_3._Schedule_of_Activities.pdf.

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