Trials

STUDY PROTOCOL

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Role of the screening with coronary computed tomography angiography on lipid management and risk factors control in an asymptomatic Chinese population: a community-based, parallel-group, open-label, randomized clinical trial (RESPECT2)

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Abstract

Background Lipid management based on cardiovascular risk level is the cornerstone of primary prevention of coronary artery disease (CAD), while the accuracy and adherence of traditional cardiovascular risk stratification have been questioned. Prevention strategies based on imaging screening for atherosclerotic plaques are found to be more objective and adherent in recent studies. This trial aims to investigate the role of coronary computed tomography angiography (CCTA) in guiding the primary prevention of CAD in a randomized controlled design.

Methods Approximately 3400 middle-aged asymptomatic community participants will be recruited and randomized in a 1:1 ratio to a traditional cardiovascular risk score-guided (usual care group) or CCTA-guided (CCTA group) strategy. Participants with cardiovascular disease, prior lipid-lowering therapy, CCTA contraindication, or serious diseases that affect life span will be excluded. The intervention strategy includes blood pressure, blood glucose, and lipid management and lifestyle modifications. Blood pressure and glucose targets and lifestyle modification recommendations keep the same in both strategies, while lipid management is personalized based on traditional risk level or CCTA results, respectively. The primary outcome is the proportion of participants taking lipid-lowering medication regularly at both 6 and 12 months. The secondary outcomes include the proportion of participants achieving low-density lipoprotein cholesterol lowering targets at 12 months, mean changes in lipid levels from baseline to 12 months, barriers to adherence, adverse reactions related to CCTA examination, and cardiovascular events.

Discussion The study is the first randomized clinical trial to examine the effectiveness of a CCTA-guided versus a traditional risk score-guided primary prevention strategy in an asymptomatic community-based population.

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Keywords Cardiovascular disease, Primary prevention, Lipid management, Coronary computed tomographic angiography, Community population

Introduction

Coronary artery disease (CAD) is the leading global single largest killer in the world and the prevalence of CAD is increasing in China. The main reason for this reality is the low and non-sustained adherence to prevention guidelines among practitioners and individuals. In the current guidelines, lipid management based on the cardiovascular risk level is the cornerstone of primary prevention of CAD [1, 2]. However, evidence showing that the use of these traditional risk estimation systems translates into reduction of cardiovascular disease (CVD) morbidity or mortality is scarce [3]. One of the reasons for the failure of prevention is that current traditional risk estimation systems are not accurate, because they only consider major causal risk factors at one single time point to classify individuals into different risk categories and ignore individual heterogeneity and the cumulative exposure of risk factors over time.

Medication adherence is another important factor affecting the risk of CVD [4]. Unfortunately, statin adherence is far from optimal treatment over time [5]. In China, a national study of 1.7 million people found that 1 in 10 participants had a high risk for CVD, and among those at high CVD risk, only 0.6% were under statin treatment [6]. Regardless of the knowledge about the nature of lipid-lowering drugs, misunderstanding or misperception of traditional risk levels by asymptomatic population is an important reason for this phenomenon [7, 8]. In other words, the traditional risk information might be too abstract and therefore fail to communicate appropriate pharmacological prescription and enhance motivation for a healthier lifestyle. Patient perception and understanding of CVD risk through clear or even visualized evidences are essential to optimizing adherence to both pharmacotherapy and lifestyle modification [9].

Coronary computed tomography angiography (CCTA) is the only non-invasive tool capable of robustly imaging the coronary atherosclerotic plaque that leads to CAD. Due to its high accuracy and negative predictive value, CCTA is recommended by multiple guidelines for routine clinical practice in patients with acute and chronic chest pain [10–12]. Meanwhile, with the update of CT equipment and the optimization of CCTA technology, the radiation dose of CCTA can reach less than 1 mSv with preserved image quality [13], which makes CCTA a safe and effective tool to screen subclinical CAD in an asymptomatic population. In addition, some recent studies have shown that, due to the advantages of accuracy, objectivity, and easy to read, imaging-based atherosclerosis screening strategies can significantly improve population adherence to lipid-lowering drugs [14, 15]. Therefore, in theory, CCTA can solve the two core problems, i.e., inaccurate risk stratification and low medication adherence, in the CAD primary prevention. However, there is no randomized controlled trial to confirm the role of CCTA in primary prevention of CAD in a general population [16]. Based on the above-mention reasons, we choose traditional cardiovascular risk score-guided strategy and CCTA-guided strategy as comparators in this study.

Besides, knowledge of the prevalence and characteristics of CAD in the asymptomatic general population is a prerequisite for constituting high-risk screening strategies. For example, the prevalence of subclinical CAD screening by CCTA in middle-aged and elderly asymptomatic population in Europe and the USA ranges from 42 to 49% [17–19]. However, little is known about subclinical CAD in Chinese middle-aged and elderly asymptomatic population.

Therefore, we will conduct a randomized clinical trial with two parallel groups and a 1:1 allocation to the usual care arm or the CCTA arm in an asymptomatic community population aged 40 ~ 69 years, with the aims of (1) evaluating whether the strategy based on CCTA is superior to traditional cardiovascular risk score in improving lipid management in an asymptomatic community population and (2) determining the prevalence of subclinical CAD in a Chinese middle-aged and elderly asymptomatic population.

Methods

Study design

RESPECT2 trial is an investigator-initiated, prospective, community-based, open-label, and pragmatic randomized controlled trial. The primary objective is to assess the effect of the CCTA-guided prevention strategy (CCTA group) on lipid management versus usual care (usual care group) in the asymptomatic population. The second study objective is to determine the prevalence of subclinical CAD among middle-aged and elderly (40 ~ 69 years) asymptomatic community individuals in Nanjing, China. A study flowchart is displayed in Fig. 1.

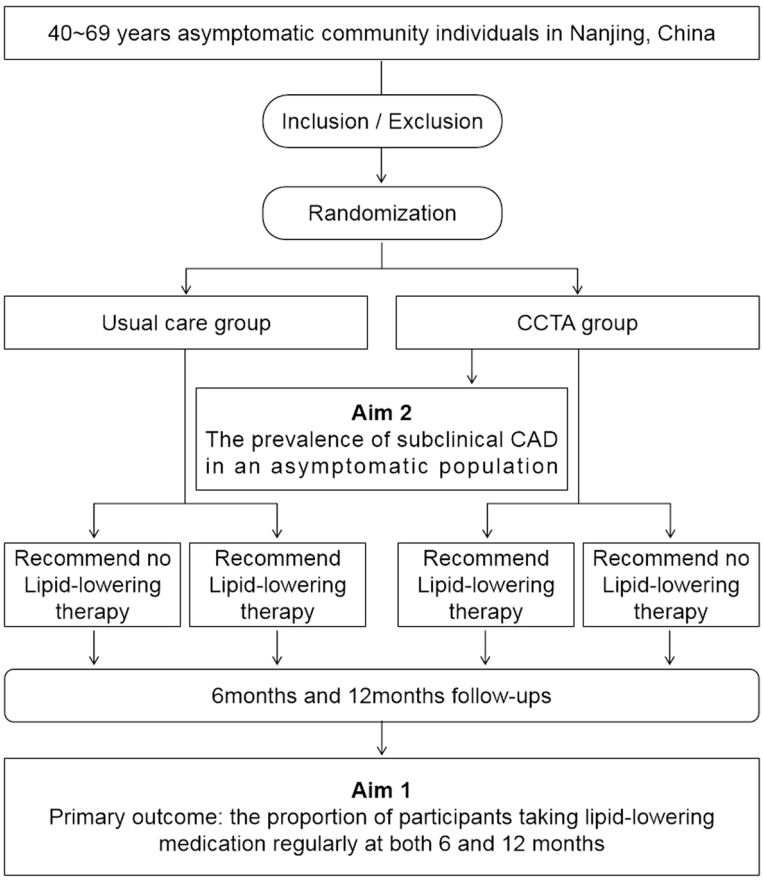

Fig. 1 The flow chart of the trial. CCTA, coronary CT angiography. CAD, coronary artery disease

Eligibility criteria

This study will recruit 40 ~ 69 year-old asymptomatic community individuals in Nanjing, China. Study recruitment will be based on volunteer participation and carried out by investigators. The study will be publicized to targeted groups in community members of 11 municipal districts throughout Nanjing (see S1 in the Supplementary Appendix). The complete trial inclusion and exclusion criteria are shown in Table 1.

Table 1 Study enrollment criteria

Inclusion criteria
■ Nanjing residents who have no plans to leave in the next 5 years
■ Aged from 40 to 69 years
■ Free of any known clinically cardiovascular disease
■ Able to comprehend and sign an informed consent form
Exclusion criteria
☐ Serious liver dysfunction, defined as AST or ALT > 3 times the normal upper limit
☐ Chronic kidney disease (CKD) > stage 4, defined as eGFR < 30 ml/min/1.73 m^2
☐ Prior CCTA or invasive coronary angiography within the last 5 years
☐ Any contraindications for CCTA
☐ Previous use of statin or non-statin lipid-lowering medication (such as ezetimibe, PCSK9 inhibitor, and Xuezhikang)
☐ Life expectancy < 3 years
☐ Other reasons the researcher deems inappropriate to attend

AST Aspartate aminotransferase, *ALT* Alanine transaminase, *eGFR* estimated glomerular filtration rate, *CCTA* Coronary computed tomography angiography, *PCSK9* Proprotein convertase subtilisin kexin type 9

Screening, enrollment, and randomization

Screening will be conducted in 2 steps. First, participants will be enrolled if they meet all general inclusion and exclusion criteria in the form of self-reports and providing written informed consent. Subsequently, the baseline examination will be collected. Second, enrolled participants will be screened again for laboratory index (excluding participants with serious liver dysfunction or eGFR < 30 ml/min/1.73 m^2, etc.).

The data monitoring committee (DMC) is responsible for generation of allocation sequence. Participants meeting all entry criteria will be then randomly assigned in a 1:1 ratio to the CCTA group or the usual care group, and randomization is stratified by CVD risk stratification

(low, moderate, and high risk) which is determined according to the Chinese guideline for lipid management 2023 [20] (Supplemental Fig. 1). In addition, randomization will be generated into blocks, while block sizes will not be revealed to researchers. The randomization sequence will be generated by an independent statistician using the R software version 4.1.2.

Blinding

Although the blinding of participants or clinicians in this study is not possible because the comparator is usual care, the online randomization service will ensure allocation concealment until the participants are recruited into the trial and after all baseline measurements are completed. The primary outcomes will be adjudicated by an independent clinical adjudication committee blind to allocation of intervention.

Study interventions and treatments

If the participant is assigned to the usual care group, lipid-lowering strategy will be developed based on the CVD risk stratification according to the guideline [20]. If the participant is assigned to the CCTA group, CCTA will be performed first. Then, lipid-lowering strategy will be developed based on CCTA results that indicate the presence or absence of coronary artery plaque. All participants of both groups will receive cardiology clinic counseling and advice. There will be no special criteria for discontinuing or modifying allocated interventions. Besides, implementing CCTA or usual care will not require alteration to usual care pathways (including use of any medication), and these will be permitted to continue for both trial arms. The details of the cardiovascular primary prevention algorithm are described as follows.

Firstly, participants will be divided into four categories: apparently healthy participants, the participants with diabetes mellitus, CKD stage 3 (defined as eGFR 30 ~ 59 ml/min/1.73 m^2), and severe hyperlipidemia [defined as low-density lipoprotein cholesterol (LDL-C) ≥ 4.9 mmol/L or total cholesterol (TC) ≥ 7.2 mmol/L]. Secondly, four categories of participants will be divided into low risk (< 5%), medium risk (5 ~ 9.9%), or high risk (≥ 10%) degree. Blood pressure control target is set at < 140/90 mmHg and glycosylated hemoglobin A1c (HbA1c) < 7.0% in all subjects. In terms of lipid management, with LDL-C as the control target, the recommended lipid-lowering drug regimen and set target values are as follows (Fig. 2a, b).

Usual care group

1) Apparently healthy participants. For low-risk population, lipid-lowering drugs will not be recommended, and LDL-C target value is < 3.4 mmol/L; for medium risk population, the LDL-C target value is < 2.6 mmol/L, lipid-lowering drugs will be recommended when LDL-C is > 2.6 mmol/L, and when LDL-C is ≤ 2.6 mmol/L, lipid-lowering drugs will not be recommended; for high-risk population, lipid-lowering drugs will be recommended with LDL-C target values of < 2.6 mmol/L.
2) Diabetes mellitus (≥ 40 years old). Lipid-lowering drugs will be recommended with LDL-C target values of < 1.8 mmol/L.
3) CKD stage 3. Lipid-lowering drugs will be recommended with LDL-C target values of < 2.6 mmol/L.
4) Severe hyperlipidemia. Lipid-lowering drugs will be recommended with LDL-C target values of < 2.6 mmol/L.

CCTA group

1) Apparently healthy participants. For participants without CAD, lipid-lowering drugs will not be recommended, and the LDL-C target value is < 3.4 mmol/L, while for participants with CAD, lipid-lowering drugs will be recommended with LDL-C target values of < 1.8 mmol/L.
2) Diabetes mellitus (≥ 40 years old). For participants without CAD and target organ damage, lipid-lowering drugs will be recommended with LDL-C target values < 2.6 mmol/L, while for participants with CAD or combined with target organ damage, lipid-lowering drugs will be recommended with LDL-C target values < 1.8 mmol/L.
3) CKD stage 3. For participants without CAD, lipid-lowering drugs will be recommended with LDL-C target values < 2.6 mmol/L, while for participants with CAD, lipid-lowering drugs will be recommended with LDL-C target values < 1.8 mmol/L.
4) Severe hyperlipidemia. For participants without CAD, lipid-lowering drugs will be recommended with LDL-C target values < 2.6 mmol/L, while for participants with CAD, lipid-lowering drugs will be recommended with LDL-C target values < 1.8 mmol/L.

In addition, for CAD patients with non-significant coronary stenosis (> 0% and < 50% diameter stenosis in any coronary artery [> 1.5 mm]), if it is difficult to reduce LDL-C below 1.8 mmol/L, a 50% reduction from baseline will be targeted as an alternative indicator. On the other hand, for CAD patients with significant coronary stenosis (≥ 50% diameter stenosis of any coronary artery [> 1.5 mm]), the lipid lowering goal is to reduce LDL-C to less than 1.8 mmol/L and reduce

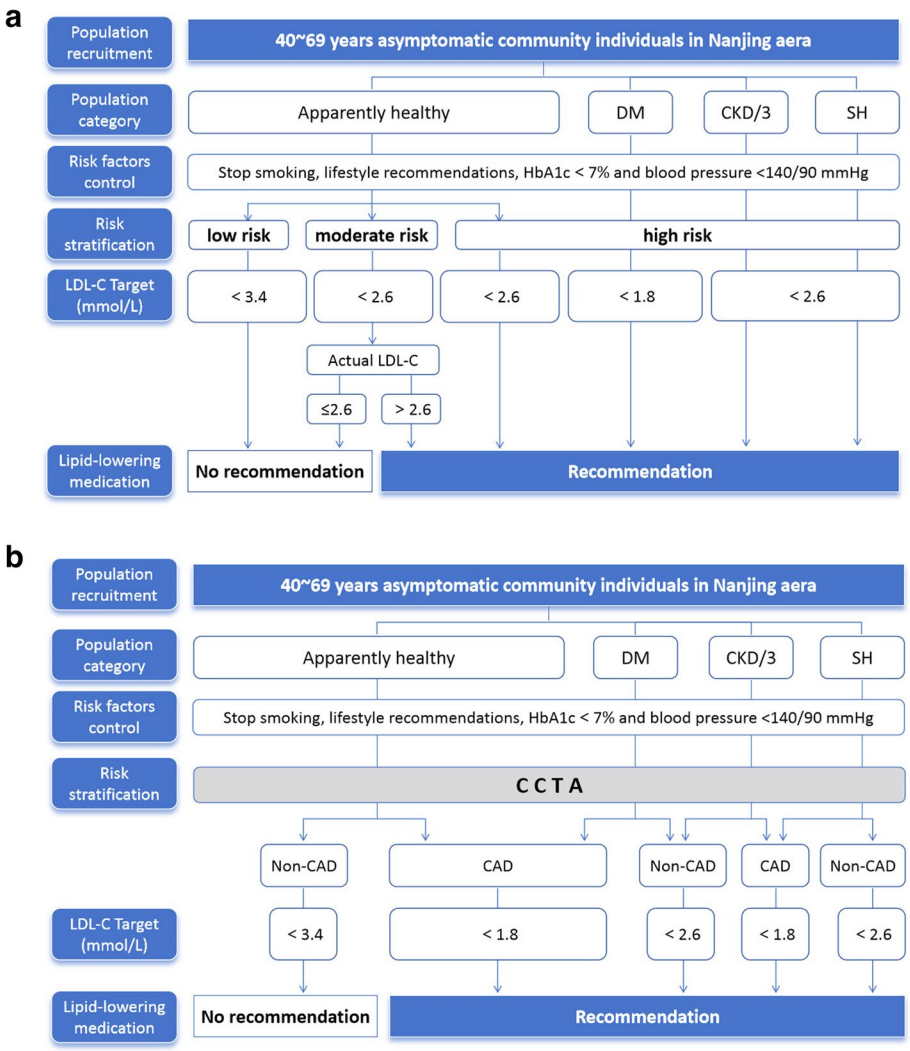

Fig. 2 **a** Primary prevention algorithm of usual care group. **b** Primary prevention algorithm of CCTA group. DM, diabetes mellitus; CKD/3, chronic kidney disease stage 3; SH, severe hyperlipidemia; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; CCTA, coronary computed tomography angiography; Non-CAD, no coronary artery disease; CAD, coronary artery disease

50% from baseline. Furthermore, the patients (significant CAD) will receive further intervention from cardiologists, such as aspirin, or even percutaneous coronary intervention.

Follow-up

After randomization and intervention, participants will be followed up at 6 months over phone and 12 months in-person. After that, we plan to conduct annual follow-up (at least 5 years) for the participants. At each visit, data on treatment compliance (see S2 in the Supplementary Appendix), concomitant use of other drugs, onset of cardiovascular or non-cardiovascular events, and occurrence of any other adverse events will be gathered by the investigators. The laboratory tests, including serum lipid, ALT, AST, and creatine kinase will also be collected if available. At the end of the study, all events and adverse events will be reconfirmed for all patients to ensure that case-report forms are accurate.

In order to ensure that participants can be contacted, we will get 4 contact methods at baseline, including the phone number of the participant himself or herself, at least one of the participant's family members, and the social software, such as WeChat and the medical chain platform. For those participants for whatever reason could not be contacted to assess for primary endpoint data, after documentation of 3 unsuccessful attempts (on 3 different days over a 1-month period) by the follow-up specialists, we will seek help from the staffs in the participant's community. If all of the above methods fail, the subject will be considered lost to follow-up.

End points

The primary outcome is the proportion of participants taking lipid-lowering medication regularly at both 6 and 12 months. Taking lipid-lowering medication is regularly defined as taking the established lipid-lowering medication (including statin, ezetimibe, Xuezhikang, and PCSK9 inhibitor) at least 24 days during the past 30 days (≥80% days) (see S3 in the Supplementary Appendix). To validate outcomes, we will contact participants through social media (i.e., WeChat or medical chain platform) to collect prescriptions, drug packages, and drug payment records. Meanwhile, we will record the follow-up calls as traceable files.

The secondary outcomes are as follows:

a. The major secondary outcome: the proportion of participants achieving LDL-C targets at 12 months (the LDL-C treatment goals are made according to Chinese guideline [20])
b. Other secondary outcomes: the proportion of participants taking lipid-lowering medication regularly at 12 months; the mean changes in TC and LDL-C from baseline to 12 months; assessing barriers to adherence; safety; changes in renal function following CCTA examination; cardiovascular events; health economics analysis

Data collection

The study data will be collected at baseline visit and follow-up visits (Table 2). The baseline study examination includes the following: (1) a detailed assessment of self-reported cardiovascular risk factors, including demographic characteristics, medical history, medication use, lifestyle characteristics, and psychosocial factors; (2) physical exams, which include blood pressure, heart rate, height, sitting height, weight, waist circumference, and hip circumference; (3) laboratory tests, such as glucose, glycated hemoglobin, lipids [including TC, LDL-C, HDL-C, lipoprotein(a), etc.], liver and renal function, creatine kinase, homocysteine, high sensitivity C-reactive protein (hsCRP), and routine blood biochemical indexes; (4) this trial involves collecting blood sample for storage; (5) CCTA examination (only for CCTA group). The study data include both eCRF questionnaires and paper-based physical examination indexes (see S4 in the Supplementary Appendix). The data will be collected, coded, and entered to the online EDC system by the trial investigators to ensure that the data would not be tampered. The researchers will be divided into entry and review work to ensure that the data are accurate. To ensure privacy, the data of the participants will be anonymized and each participant will be assigned an ID number to hold personal information and contact details. This will be stored confidentially before, during, and after the trial.

Data on self-reported adherence and adverse events will be collected at each follow-up visit. The detailed assessment of self-reported cardiovascular risk factors, physical exams, and laboratory analyses will be collected again at 12 months (all participants). Self-reported adherence to medications will be recorded as the number of

Table 2 Participant timeline

Study period	Baseline	Allocation	Post-allocation		
			Treatment	6 month	12 month
Enrollment					
Eligibility screen	×				
Informed consent	×				
Allocation		×			
Interventions					
Usual care group			×		
CCTA group			×		
Assessments					
Questionnaire	×				×
Anthropometric measurements	×				×
Blood pressure	×				×
Biochemistry profile	×			#	×
CCTA	☆				
Primary outcome				×	×
Secondary outcomes				×	×
Adverse events				×	×

×means all participants are required, # means will be collected if available, *CCTA* coronary CT angiography, ☆ means only the CCTA group are required

days medication is missed in the month prior to the visit (value between 0 and 30 days). The type and intensity of lipid-lowering drugs will also be documented. Besides, during trial contacts, the research team will record barriers to adherence and reasons for stopping recommended medications for each participant.

Adverse event (AE) monitoring will begin when a participant is randomized and will continue for 1 year. We will record AEs which are defined as serious or which are potentially related to the intervention according to CCTA examination independently. There is no anticipated harm and compensation for trial participation.

CCTA examination and image analysis

CCTA scans will be performed using two 64-detector CT scanners. CCTA protocol optimizations will be performed throughout the study to optimize scanning parameters, such as radiation dose and contrast agent administration. Sublingual glyceryl trinitrate will be administered immediately prior to CT scan. Coronary artery calcium score (CACS) will be performed prior to CCTA according to the standard protocol. CCTA will be conducted using pre-specified protocols during a single breath hold triggered by prospective electrocardiographic gating as appropriate.

All CCTA images will be assessed independently by at least two trained observers referring to the CAD-RADS system [21]. Where there is disagreement between paired observers, CCTA will be reviewed and classified by consensus. All coronary arteries greater than 1.5 mm in diameter will be graded for stenosis severity. Non-CAD is defined as that the coronary arteries have no any visualized plaque and stenosis. CAD will be graded according to the degree of maximal coronary stenosis as (1) minimal stenosis (1–24%), (2) mild stenosis (25–49%), (3) moderate stenosis (50–69%), (4) severe stenosis (a, 70–99% stenosis, or b, left main truck ≥ 50% or 3 major epicardial vessels ≥ 70%), and (5) total coronary occlusion (100%). In this study, obstructive CAD is defined as having ≥ 50% diameter stenosis in at least one major epicardial vessel. Conversely, non-obstructive CAD is defined as encompassing both minimal and mild stenosis.

Sample size

Based on the reported prevalence and treatment rate of dyslipidemia as well as the 10-year CVD risk levels among Chinese general population [6, 22–25], we make the following assumptions: after recommendation of lipid-lowering drugs, the highest utilization rate of lipid-lowering drugs is 4 ~ 5% in the control group [the proportion of "medium–high risk" aged 40–69 years in Chinese community is 40 ~ 50%, and the highest utilization rate of recommended lipid-lowering drugs is 10% (4–10%)]. The lowest expected utilization rate of lipid-lowering drugs is 8% after the intervention with CCTA screening (assuming the prevalence of subclinical CAD is 40 ~ 50%, with an expected utilization rate of 20% for those with recommended lipid-lowering drugs). A total of 2836 evaluable participants will be required (1418 per arm) to have 90% power to detect a 3% (8% versus 5%) difference in rates of taking lipid-lowering medication regularly based on two-sided $p < 0.05$. With a 15% attrition rate, the sample size will be about 3400 participants (1700 per arm).

Meanwhile, in order to determine the prevalence of subclinical CAD in the general population, we set the CCTA group in this study as the screening population. Assuming the prevalence of subclinical CAD confirmed by CCTA in an asymptomatic population aged 40 ~ 69 years in Nanjing city is 40 ~ 50% [17–19], the tolerated absolute error of 3% with a confidence level of 95%. The sample size calculated should be of 1056 ~ 1098 participants, which is much smaller than the number of participants in the CCTA group above. Confidence interval is calculated using a Z test with a 2-sided significance level of 0.05.

Statistics

The primary analysis will be performed according to intention-to-treat principle. We will also perform sensitivity analyses of the primary and major secondary end points, including per-protocol analysis, as-treated analysis, imputation of missing primary and major secondary endpoint data under the scenarios of worst possible outcome, best possible outcome, and multiple imputation. The intention-to-treat population will consist of participants undergoing randomization. The per-protocol population will consist of participants who will be successfully randomized and undergo the treatment strategy excluding those with major protocol deviations. The as-treated population will consist of participants who will be analyzed according to the actual strategy used for treatment rather than their randomization assignments.

Type I error rate will be controlled by use of a hierarchical (fixed-sequence) testing procedure for the primary and major secondary end points, which will be tested in a predefined order (the proportion of participants taking lipid-lowering medication regularly at both 6 and 12 months, the proportion of participants achieving LDL-C lowering targets at 12 months), all at the same significance level alpha ($\alpha = 0.05$).

The modified Poisson regression model with robust error estimation will be used to estimate the risk ratio and 95% confidence interval (CI) associated with treatment effect in the analysis of prespecified primary end point and other dichotomous end points, with adjustment for prespecified covariates. Mean changes in TC

and LDL-C levels from baseline to 12 months will be analyzed using linear regression models. Plots of the cumulative incidence curves for cardiovascular events will be provided using Kaplan–Meier estimates. Estimates of the hazard ratios and 95% CI of cardiovascular events will be calculated using a Cox proportional hazards model. These models will be adjusted for stratification variables. Subclinical CAD prevalence will be estimated using the Wald method and corresponding 95% CIs are provided.

For all primary analyses, 2-sided *P* values less than 0.05 will indicate statistical significance. Because of the potential for type I errors due to multiple comparisons, the findings from the analyses of secondary outcomes will be interpreted as exploratory. All statistical analyses will be performed using the SAS software, version 9.4 (SAS Institute), by independent statisticians masked in the allocation of the treatment group.

Organization and ethical concerns

The study is an investigator-initiated, institutionally sponsored study, and therefore, the authors are solely responsible for the design and conduct of this study as well as data analysis and drafting of publications.

The steering committee (SC) is the main decision-making committee of the trial and has final responsibility for the medical and scientific conduct of the trial. The clinical events committee (CEC) is responsible for adjudicating all primary and secondary endpoints and consists of 2 experienced cardiologists, 1 experienced neurologist, 1 radiologist, and 1 statistician. The DMC includes cardiologists and statisticians. The DMC will regularly monitor the safety of the subjects enrolled in the study. Based on their clinical judgment, the DMC can recommend stopping the trial. No members of the CEC or DMC will participate in recruitment or data collection. The sponsor will not play any part in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

In addition, data collected during the course of the research will be kept strictly confidential and only accessed by members of the trial team. At present, there is no plan to share the data with other teams or organizations. The datasets analyzed during the current study will be available from the corresponding author on reasonable request. Results will be disseminated via a peer-reviewed report to the sponsor, which will be freely available, and through open access journal articles and conference presentations. The study will designate researchers, for example, JJ and RZ to obtain informed consent and formally recruit. On the consent form, participants will be asked if they agree to use of their data should they choose to withdraw from the trial. This trial will involve collecting blood sample for storage. Informed consent forms will be available from the corresponding author on request. If it is necessary to amend protocol, we will notify the sponsor and funder. Any deviations from the protocol will be fully documented using a breach report form, and the amendment of protocol will be updated in the clinical trial registry.

The study will be conducted in accordance with the ethical principles of the Declaration of Helsinki (2013) and Good Clinical Practice for Medical Devices (GCP, 2016). The study protocol, the written informed consent form, and other relevant documentation have been approved by the institutional ethics committee. It is the responsibility of the sponsor (the study PI) to ensure that written informed consent is obtained and to report serious adverse events occurring during the study to the institutional ethics committee at Nanjing Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University. Informed consent materials will be available upon request from the principal investigator. All study members will be well trained by standard operation procedures.

Discussion

CVD is the leading cause of global mortality and nearly 80% of global CVD deaths occur in low- and middle-income countries where CVD and risk factor burden are on the rise as a result of an ongoing epidemiological transition [26, 27]. Therefore, cardiovascular risk factor control is an enormous global problem that demands innovative screening and prevention strategies.

In recent years, precise prevention strategies based on noninvasive imaging plaque screening have been repeatedly proposed. Non-invasive imaging can detect the presence, extent, and composition of the atherosclerotic plaque directly, all of which are determinants of CVD events. So far, a few studies have shown that providing visualized imaging evidence of arteriosclerosis can improve cardiovascular risk factors control and medication adherence compared to usual care in asymptomatic populations [28–33]. However, these studies were conducted in specialized populations with certain cardiovascular risk factors, such as diabetes mellitus, smoke, and family history of premature CVD or CACS > 0. Whether noninvasive imaging is superior to traditional cardiovascular risk score in primary prevention in the general population has not been proven. Besides, most previous studies used CACS or carotid ultrasound which can measure carotid intimal thickness as an imaging screening tool, which is considered to be a low-intensity intervention impact on the downstream therapeutic regimen

of the prevention strategy in comparison to CCTA [8, 34, 35]. However, in asymptomatic subclinical CAD patients, CCTA is the only tool that can detect and characterize non-calcified plaque, which is not only frequently present in a relatively young population but also strongly associated with serious adverse cardiovascular events [36]. Based on the cornerstone of CAD prevention that lipid-lowering therapy is the most effective treatment for stabilizing and regressing coronary plaques [37–41], RESPECT-2 selected the use rate of lipid-lowering drugs regularly as the primary outcome of this study. To validate outcomes, the study will adopt a variety of safeguards, including telephone follow-up recordings, photos of pill box prescription, and payment records. In addition, we had registered another randomized controlled trial to demonstrate the long-term effects of CCTA screening in the primary prevention of coronary heart disease [42].

This study is also designed to obtain the prevalence of subclinical CAD among middle-aged and elderly general population in Nanjing, an important central city in China. Due to ethnic and regional differences, the composition of CVD in China is probably different from that in Western countries. The assessment and characterization of subclinical CAD burden and severity in the general population in Nanjing will be of great help for China and Asian countries to develop more appropriate prevention strategies. However, data on the prevalence of subclinical CAD in the general population is lacking in Asia.

In conclusion, the purpose of this study is to answer the following issues: (1) whether CCTA is superior to traditional cardiovascular risk score for guiding prevention strategy on lipid management and risk factors control in an asymptomatic population and (2) what is the burden and characteristics of subclinical CAD in the middle-aged and elderly general population in China. This study will be a huge step forward in the concept of CAD primary prevention based on precision imaging plaque screening.

Trial status

The protocol version number is 3.0, and the amendment date is 18 March 2024. Recruitment of patients and data collection started in June 2023. Recruitment of patients will be finished before September 2024. The 12-month follow-up will be completed before September 2025.

Abbreviations

ASCVD	Atherosclerotic cardiovascular disease
CVD	Cardiovascular disease
CCTA	Coronary computed tomography angiography
CAD	Coronary artery disease
DM	Diabetes mellitus
CKD	Chronic kidney dysfunction
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
CACS	Coronary artery calcium score

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-024-08469-z.

Supplementary Material 1: Supplementary S1. Recruitment strategies. Supplementary S2. Strategies to improve adherence to intervention protocols. Supplementary S3. Reason and rationale for setting primary endpoints. Supplementary S4. Details of data collection. Supplementary Figure 1. Classification of low, medium, high risk of ASCVD according to Chinese guidelines for lipid management 2023.

Supplementary Material 2.

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Authors' contributions

LJZ, XG, and JL contributed to the study conception, design, and supervision. XG drafted the article, modified by LJZ. HG, YW, and YL performed the statistical analysis. YZ, YL, JJ, RZ, WX, JM, CL, JY, YL, MZ, DT, XW, JS, BW, CW, JZ, DY, XB, JC, and YC contributed to the acquisition of data. PJ, JZ, CZ, and XC disseminated the project. All authors read and approved the final version of the manuscript.

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Declarations

Ethics approval and consent to participate

The study protocol has been approved by the ethics committee of the Jinling Hospital, Affiliated Hospital of Medical School, Nanjing University. We will obtain written informed consent from each patient before they are randomized.

Consent for publication

Informed consent will be obtained and the model consent form can be made available. No identifying images or other personal or clinical details of participants will be presented in reports of the trial results.

Competing interests

The authors declare that they have no competing interests.

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