Study Protocol

Assessing the impact of evolocumab on thin-cap fibroatheroma and endothelial function in patients with very high-risk atherosclerotic cardiovascular disease: a study protocol for a randomized controlled trial

Bingyu Gao^, Nan Nan, Mingduo Zhang, Jinfan Tian, Yanlong Ren, Yuguo Xue, Min Zhang, Xiantao Song*, Changjiang Ge*

Department of Cardiology, Beijing An Zhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing Engineering Research Center of Cardiovascular Wisdom Diagnosis and Treatment, Beijing, China

Contributions: (I) Conception and design: B Gao, N Nan; (II) Administrative support: Min Zhang, X Song, C Ge; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: B Gao, N Nan, Mingduo Zhang, J Tian, Y Ren, Y Xue, Min Zhang; (V) Data analysis and interpretation: B Gao, N Nan; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*These authors contributed equally to this work.

Correspondence to: Xiantao Song, MD; Changjiang Ge, MD. Department of Cardiology, Beijing An Zhen Hospital, Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, Beijing Engineering Research Center of Cardiovascular Wisdom Diagnosis and Treatment, Anzhen Rd No. 2, Chaoyang District, Beijing 100029, China. Email: song0929@mail.ccmu.edu.cn; cjge1116@163.com.

Background: The prevalence of very high-risk atherosclerotic cardiovascular disease (ASCVD) is significant in China, with suboptimal rates of low-density lipoprotein cholesterol (LDL-C) compliance exacerbating plaque instability and causing a higher incidence of major adverse cardiac events (MACEs). Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) are effective in reducing LDL-C levels, increase the stability of vulnerable plaque, and influence the progression of atherosclerosis through multiple mechanisms as demonstrated in animal studies. However, there is currently a lack of *in vivo* evidence regarding the efficacy and safety of high-intensity statin therapy combined with PCSK9i in the secondary prevention of ASCVD in the Chinese population. This study aims to demonstrate the efficacy of high-intensity statins combined with PCSK9i on vulnerable plaques in very high-risk ASCVD patients through intravascular imaging and non-invasive endothelial function test.

Methods: This randomized, open-label, prospective clinical study involves 240 patients with very high-risk ASCVD who meet the criteria outlined in the 2023 Chinese lipid management guidelines. Patients recruitment will be processed in Beijing Anzhen Hospital from January 2021 to December 2024. Patients with thin-cap fibroatheroma (TCFA) detected by optical coherence tomography (OCT) are randomly assigned in a 1:1 ratio to the evolocumab group (evolocumab 140 mg every 2 weeks plus atorvastatin 40 mg nightly) or the standard treatment group (atorvastatin 40 mg nightly). The primary endpoint is the absolute change of the minimum fibrous cap thickness (FCT) at a median follow-up of 1 year. The secondary endpoints are other OCT metrics, assessment of MACE rates, alterations in serum lipid profiles and markers of inflammation, endothelial function, and adverse drug reactions. Logistic regression, analysis of covariance (ANCOVA), Kaplan-Meier curve survival analysis, and Cox regression will be used to investigate the relationship between variables and endpoints.

Discussion: The purpose of this study is to evaluate the efficacy of high-intensity statin therapy combined to PCSK9i for the secondary prevention of coronary artery disease in Chinese patients with very high-risk ASCVD. The results will provide evidence to optimize the management of this high-risk population.

^ ORCID: 0000-0003-0372-6387.

Trial Registration: This study was registered on chictr.org.cn (ChiCTR2000032570).

Keywords: Atherosclerotic cardiovascular disease (ASCVD); optical coherence tomography; thin-cap fibroatheroma; PCSK9 inhibitors; endothelial function

Submitted Jul 15, 2024. Accepted for publication Nov 04, 2024. Published online Dec 19, 2024.
doi: 10.21037/cdt-24-336
View this article at: https://dx.doi.org/10.21037/cdt-24-336

Introduction

Background

Atherosclerosis is the major cause of mortality and poses a great threat to public health. The Chinese Lipid Management Guidelines (2023) (later referred to as the "2023 Chinese Guidelines") define very high-risk atherosclerotic cardiovascular disease (ASCVD) as having had ≥2 severe ASCVD events or 1 severe ASCVD event combined with ≥2 high-risk factors. Severe ASCVD events included a recent history of acute coronary syndrome (ACS) (<1 year), previous history of myocardial infarction (other than ACS), ischemic stroke, symptomatic peripheral vascular disease, and prior revascularization or amputation. High-risk factors include low-density lipoprotein cholesterol (LDL-C) ≤1.8 mmol/L, recurrence of severe ASCVD events, early onset coronary artery disease (CAD) (male <55 years old, female <65 years old), familial hypercholesterolemia or baseline LDL-C ≥4.9 mmol/L, previous history of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI), diabetes mellitus, high blood pressure, chronic kidney diseases (CKD) stage 3–4 and smoke (1). In China, 75.1% of the patients are classified as those with very high-risk ASCVD (2). Upon admission, only 6.6% of individuals achieved the recommended LDL-C level of <1.4 mmol/L, and 95.1% still received statin monotherapy at discharge (2,3). The 2023 Chinese Guidelines recommend that individuals with a very high risk of ASCVD who do not achieve adequate LDL-C levels with statin treatment may benefit from additional non-statin lipid-lowing drugs, such as cholesterol absorption inhibitors or proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) (1). Although the 2023 Chinese Guidelines recommend the initial use of conventional or moderate-intensity statin, available evidence suggests that high-intensity statin is beneficial to reduce the incidence of endpoint events in patients with ASCVD among the Asian population (4-7).

Rationale and knowledge gap

Numerous studies have shown that endothelial dysfunction is the main initiation factor of atherosclerosis (8-10). Patients with coronary microvascular endothelial dysfunction (CMED) exhibit more vulnerable plaque characteristics, and higher plaque burden associated with a larger necrotic core volume (11). The stability of these plaques hinges on the fibrous cap thickness (FCT), as the exposure of the lipid core to circulating blood can trigger platelet activation, leading to sudden cardiac death and ACS (12). Vulnerable plaques prone to rupture have a large lipid core, thin fibrous cap, and macrophage infiltration near the cap, known as thin-cap fibroatheroma (TCFA) (13,14).

PCSK9, which is mainly synthesized in the hepatic endoplasmic reticulum, binds to and accelerates lysosomal degradation of LDL receptor (LDLR) on the cell surface, thereby inhibiting uptake of LDL-C by hepatocytes, leading to increase of LDL-C in plasma, and accelerating the progression of atherosclerosis (15). Pre-clinical study demonstrated that locally produced PCSK9 within atherosclerotic plaques promotes monocyte infiltration and macrophage inflammation through an LDLR-dependent mechanism in a cholesterol-independent manner, thereby influencing lesion composition (16).

Recent studies have shown that PCSK9i has pleiotropic effects on atherosclerosis. Studies using multimodal imaging techniques have confirmed that the primary effect of PCSK9 inhibitors is to reduce plaque burden and alter the composition of atherosclerotic plaques by regulating lipid levels (17-19). Some preclinical and clinical studies have found that PCSK9 can directly induce inflammation and exacerbate atherosclerosis, independent of changes in lipid profiles. PCSK9 inhibitors can reduce oxidative stress, lipid deposition, and plaque lesion area, and enhance autophagy, reducing oxidative stress and inflammation in atherosclerosis (20-23). This phenomenon has also been observed in subjects with LDL-C levels <100 mg/dL,

supporting the possibility that PCSK9 inhibitors have a net anti-inflammatory effect (24). Systemic and/or vascular inflammation biomarkers play an important role in coronary plaque formation and rupture (25). About 60% of subjects in the secondary prevention for ASCVD can be defined as having a "high inflammation risk" based on C-reactive protein (CRP) levels (26). The impact of PCSK9i on systemic inflammation and local plaque inflammation will be evaluated through the analysis of circulating inflammatory biomarkers and macrophage aggregation in plaques via optical coherence tomography (OCT). Chronic vascular inflammation induces endothelial dysfunction, but the findings of current research using non-invasive diagnostic methods to assess the effect of PCSK9i on endothelial function are inconsistent. The sub-study of PACMAN-AMI found that adding PCSK9 inhibitors to high-intensity statin therapy failed to produce a further beneficial effect on flow-mediated dilation (FMD) in patients with AMI (27). However, another study found that PCSK9i significantly improved endothelial function indicators such as FMD in patients with ACS after 6 weeks (28).

OCT is an intravascular imaging modality based on near-infrared light that provides high-resolution images, which can be used to identify high-risk anatomical plaque features that have been recognized as fundamental to the pathogenesis of CADs, guiding PCI, and optimizing stent implantation (29-32). Peripheral arterial tonometry (PAT) is a novel non-invasive method that assesses endothelial and microvascular dysfunction by measuring reactive hyperemia in the microvasculature of the finger. The reactive hyperemia index (RHI) is associated with ASCVD risk and the presence of CAD (33). Compared to FMD, PAT does not require complex sensors, ultrasound systems, or highly experienced operators. It is a simpler and more cost-effective method that also offers better inter-observer reproducibility (34).

Objective

Therefore, it is hypothesized that compared with high-intensity statin monotherapy, high-intensity statin combined with PCSK9i can further increase the stability of non-criminal lesion vulnerable plaques in very high-risk ASCVD patients, improve endothelial function, and further reduce the incidence of major adverse cardiac event (MACE). This study aims to dynamically observe the characteristics of non-criminal lesion vulnerable plaques. OCT in patients with very high-risk ASCVD, clarify the relationship between "lipid, plaque and events" through *in vivo* analysis, and evaluate the efficacy and safety of high-intensity statins combined with PCSK9i lipid-lowering treatment (LLT) in Chinese population. Additionally, it also investigates the relationship between endothelial function and plaque vulnerability and the influence of different LLT on endothelial function by noninvasive endothelial function tests. We present the protocol in accordance with the SPIRIT reporting checklist (35) (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-336/rc).

Methods

Study design

This study is a single-center, parallel-group, open-label, randomized trial (version 1.0/16th September 2024). All the procedures will be conducted at Beijing Anzhen Hospital. Recruitment will take place between January 2021 and December 2024, with a median follow-up duration of one year. Due to the COVID-19 pandemic, we were affected in the study preparation phase. Considering the continuity of patient enrollment and the possible impact of the epidemic on CAD, we have postponed the enrollment to 2021. Data will be collected within one week after OCT image acquisition for each patient. This study has received approval from the Ethics Committee of Beijing Anzhen Hospital Medical (No. ks202002), which will be conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was registered at Chinese Clinical Trial Registry [ChiCTR, chictr.org.cn (ChiCTR2000032570)]. Informed consent will be obtained from all participants. The specific study timeline of this study is shown in *Table 1*.

Participants

The participants include adult patients with very high-risk ASCVD. PCI procedures are performed in all patients. *Table 2* shows the complete inclusion and exclusion criteria. All eligible patients will receive comprehensive information from the researchers and will sign an informed consent form.

Randomization and allocation

Once the eligibility is confirmed after OCT imaging and written informed consent is obtained, patients will be randomized. In order to ensure better balance between the

Table 1 Study timeline

Study phase	Task description	Time frame
Study initiation	Obtain ethical approval, register study	March 2020 to May 2020
Patient recruitment	Recruit 240 patients, obtain informed consent	January 2021 to December 2024
Randomization and intervention	Randomly assign patients, conduct 12-month intervention	January 2021 to December 2024
Follow-up	Follow-up assessments at 3, 6, 9, and 12 months post-intervention	January 2022 to December 2025
Data analysis	Data cleaning and statistical analysis	January 2026 to March 2026
Reporting and publication	Write study report, submit for publication	April 2026 to December 2026

Table 2 Study inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. At least 18 years of age	1. Previous use of any PCSK9i
2. Very high-risk ASCVD	2. Uncontrolled hypertension (SBP ≥180 mmHg; DBP ≥110 mmHg) or diabetes
3. Have a qualifying LDL-C level at the time of screening based on the use of either no statin (LDL-C ≥3.4 mmol/L) or low or moderate intensity statin (LDL-C ≥1.8 mmol/L)	3. Known allergy or contraindication to evolocumab or atorvastatin
4. Successful PCI procedure	4. Known history of hemorrhagic stroke
5. OCT detected TCFA (TCFA is defined as FCT <65 mm and lipid radian greater than or equal to 2 quadrants)	5. Undergoing cancer treatment
	6. Treated with lipoprotein monocollection of blood components
	7. Severe liver and kidney dysfunction
	8. Pregnant or lactating women
	9. For any reason, the investigator considered patients who were not suitable for this study

PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitor; ASCVD, atherosclerotic cardiovascular disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; OCT, optical coherence tomography; TCFA, thin-cap fibroatheroma; FCT, fibrous cap thickness.

experimental and control groups, block randomization will be employed, and the allocation sequence will be computer-generated to ensure randomization. Participants will be randomly assigned in a 1:1 ratio in a single-blind manner, with allocation concealment based on sequential coding. Patients will be recruited by surgeons, and randomized and allocated by researchers.

In this study, participants will be blinded to their group allocation to minimize bias regarding treatment expectations. All participants will receive the same procedure description to avoid cognitive bias caused by inconsistent information. Unblinding will only occur in the case of a medical emergency where knowledge of the participant's group assignment is essential for their care. All unblinding events will be reported and documented in the study records for transparency.

Intervention

Patients will be blindly randomized into two treatment groups: either atorvastatin 40 mg QN (p.o.) + evolocumab 140 mg Q2W (s.c.), or atorvastatin 40 mg QN (p.o.) alone (*Figure 1*). If there is an increase in creatine kinase levels ≥5 times upper limit of normal (ULN) and/or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels ≥3 times ULN, statin therapy should be discontinued. If the above indicators return to normal, statin therapy may be resumed after one month of observation; otherwise, the

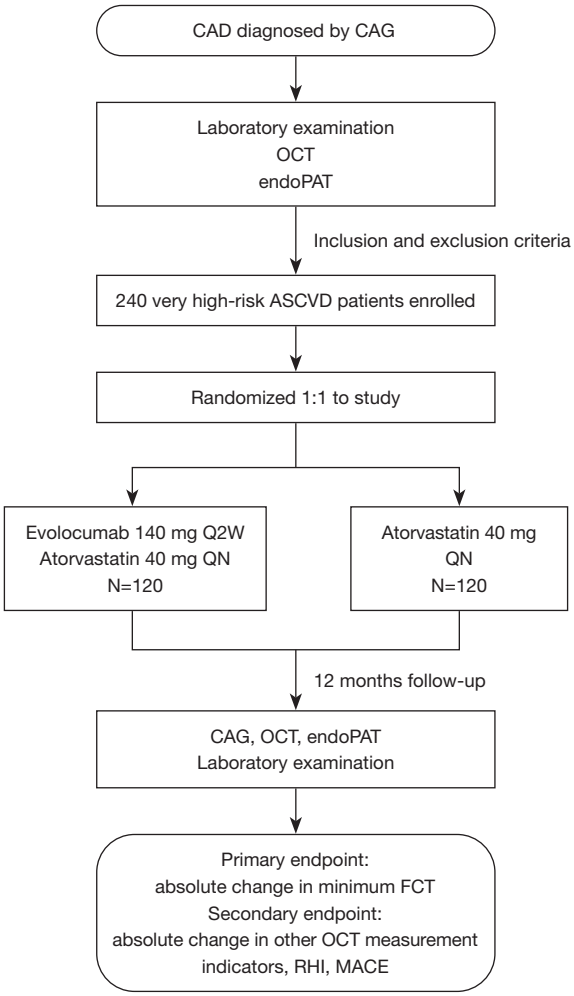

Figure 1 Study design. CAD, coronary artery disease; CAG, coronary angiography; OCT, optical coherence tomography; endoPAT, endo peripheral arterial tonometry; ASCVD, atherosclerotic cardiovascular disease; FCT, fibrous cap thickness; RHI, reactive hyperemia index; MACE, major adverse cardiac event.

treatment regimen should be discontinued. In cases where LDL-C levels drop below 0.5 mmol/L during follow-up, the investigators will decide whether to terminate the regimen.

Measures

OCT image acquisition and analysis

The ILUMIEN OPTIS OCT imaging system will be used for OCT image acquisition and analysis. Following the PCI procedure, OCT imaging will be promptly conducted in the target vessel chosen for investigation immediately. Imaging will be strictly executed during maximal vasodilatation (through repetitive administration of 100–200 μg intracoronary nitroglycerin before every pullback) throughout the procedure. OCT imaging will be obtained by positioning an Abbott Dragonfly OPTIS catheter distally and withdrawing it to the aorta at a speed of 36 mm/s via automatic pullback for a total length of 75 mm, which ensures the complete removal of blood from the targeted segment. During the procedure, the contrast agent will be flushed at a rate of 3–4 mL/s for 3–6 seconds using a ring-handle syringe. The dedicated image inspection system will be used to digitally store and analyze OCT images offline, with the image analyst blinded to the group assignment.

Baseline and follow-up OCT image series will be meticulously analyzed to align with the target lesion based on the proximity to landmarks such as bifurcation or calcification. Calibration will be employed prior to analysis. For each target lesion, additional manual corrections and automated measurement algorithms will be utilized to determine the minimum lumen area. Plaques will be classified as lipid-rich, fibrous, or fibrocalcific according to previously validated criteria. A fibrous cap will be seen as a signal-rich tissue layer overlying a region with poor signal. The minimum FCT will be measured as follows: three candidate frames will be chosen during visual screening, and the FCT will be measured at the thinnest part of each frame. The minimum FCT will be measured as the smallest value of the measurements from the candidate frames. Lipid-rich plaques will be characterized by determining the lipid-core length and lipid arc. Lipid-core length will be defined as the longitudinal length of plaque with >90° of lipid involvement. Lipid arc will be measured in a lipid-rich plaque at 0.2 mm intervals for recording the mean and maximum lipid arc. The lipid index will be calculated by multiplying the longitudinal length of the lipid core by the mean lipid arc. Macrophages, visualized by IVOCT as distinct, signal-rich, or confluent punctate regions, will be graded according to their distribution within the lesions. Macrophage grading will be performed every 0.2 mm as follows: grade 0, no macrophage; grade 1, localized macrophage accumulation in the lesion with a cross-sectional area <30°; grade 2, clustered accumulation covering an area of 30° to <90°; grade 3, clustered accumulation covering an area of 90° to <270°; grade 4, clustered accumulation in an area >270°. All qualitative and quantitative OCT parameters that describe continuous vascular changes will be compared between groups.

Three blood vessels will be scanned by OCT. OCT imaging will be performed on plaques with non-left main artery and non-culprit lesions with a visual angiographic estimate of 20–70% diameter stenosis. If there are more than two eligible lesions, the lesion with the most severe stenosis will be selected as the target lesion for OCT analysis. OCT image analysis will be performed back to back by two experienced OCT technicians. Any inconsistency in measurement results will be checked by a third technician.

Endothelial function test

The non-invasive peripheral endothelial function test will be utilized to evaluate endothelial function in eligible patients at baseline and at 12-month follow-up. The RHI will be measured using the EndoPAT 2000 Machine (Itamar Medical Ltd., Caesarea, Israel). Patients will be required to fast for 8 hours, abstain from tobacco, alcohol, and caffeine, and refrain from exercise for 8 h before testing. Administration of nitrates or any other medication for erectile dysfunction should be halted one day prior to the endothelial function test for each patient. The test will be conducted in a quiet, dimly lit, and temperature-controlled environment. An occlusion cuff will be positioned above the elbow on the left arm, and fingertip plethysmograph probes will be positioned on the index finger of each hand. Throughout the test duration, pulse wave amplitude will be continuously recorded by the device. The protocol will commence with a 5-minute baseline period, followed by 5 minutes of the cuff's rapid inflation to a supra-systolic pressure of 60 or 200 mmHg to achieve complete brachial artery occlusion. Subsequently, reactive hyperemia will occur during the last 5 minutes after cuff release. Trained physicians will perform the tests (36,37).

Follow-up

Patients will be followed up by telephone or clinical visit every 12 weeks after PCI, with optimal medical therapy for a median of one year. Health and mental status will be assessed by the Seattle Angina Pectoris Questionnaire (SAQ), Patient Health Questionnie-9 (PHQ-9), Generalized Anxiety Disorder Questionnie-7 (GAD-7), and Short-From-36 Health Survey (SF-36). One year after PCI, all patients will be required to have a clinical visit for coronary angiography and OCT imaging. The visit schedule is shown in *Table 3*.

Endpoints

The primary endpoint is the absolute change of the minimum FCT in a matched arterial segment from baseline to month 12. The secondary endpoints are the absolute change of minimum lumen area, overall macrophage accumulation grade, lipid index, mean lipid arc and RHI from baseline to month 12. Exploratory endpoints include the incidence of MACEs. This study will also observe adverse drug reactions, including injection site reactions, myalgia, neurocognitive events, and severe bleeding events (cerebral hemorrhage, gastrointestinal hemorrhage).

Data collection

Data collection will be performed via a pre-designed case report form. Data elements include patient demographics, medical histories, medications, admission conditions, laboratory results, coronary angiography, OCT imaging results, endothelial function tests, and clinical events (*Table 4*).

Statistical methods

The assumption in the calculation of sample size is based on the primary endpoint of HUYGENS study (38). The change of minimum FCT at 50 weeks is 21.5±48.67 μm for the placebo group, and 42.7±47 μm for the evolocumab group. Assuming a 10% loss of follow-up rate, 120 patients in each treatment group are asked to provide 90% power at a 2-sided α of 0.05. The sample size is calculated using the two-sample T-tests method of pass15.0 statistical software (NCSS, USA).

Categorical variables will be defined as frequency counts and compared using Fishers exact test or chi-square test. Continuous variables will be defined as mean±standard deviation (SD) or median with corresponding interquartile range (IQR). Shapiro-Wilk test and Kruskal-Wallis test will be used for normality tests. Differences in continuous data will be compared using the Mann-Whitney *U* test or Student's *t*-test. The univariable and multivariable logistic regression will be employed to assess the relationship between baseline FCT and clinical measures. The analysis of covariance (ANCOVA) will be employed to analyze the primary and secondary endpoints for the covariates of patient demographics, treatment groups, conventional cardiovascular risk factors, and baseline LDL-C. Kaplan-Meier curve survival analysis will be used to compare the effects of different. LLT strategies on MACE at 12-month follow-up. To identify predictors, the effects of OCT

Table 3 Visit schedule

Evaluation	Screening	Baseline	Follow-up			
	V0	V1	V2 3 months	V3 6 months	V4 9 months	V5 12 months
Visit window	–3 to 1 d	–1 to 0 d	±7 d	±7 d	±7 d	±7 d
Informed consent	×					
Demographic data	×					
Medical histories	×					
Symptoms	×		×	×	×	×
Vital signs		×	×	×	×	×
Physical examination		×	×	×	×	×
NYHA functional class	×		×	×	×	×
ECG		×				×
UCG		×				×
Blood routine		×	×	×	×	×
Coagulation function		×	×	×	×	×
Platelet function		×				×
Liver and kidney function		×	×	×	×	×
Myocardial enzyme		×	×	×	×	×
BNP/NT-proBNP		×				×
FBG		×				×
HBA1c		×				×
Lipid profile	×	×	×	×	×	×
Coronary angiography	×	×				×
OCT imaging	×	×				×
Endothelial function		×				×
SAQ		×	×	×	×	×
SF-36		×	×	×	×	×
PHQ-9		×	×	×	×	×
GAD-7		×	×	×	×	×
MMAS-8		×	×	×	×	×
Medications		×	×	×	×	×
MACE			×	×	×	×

X indicates that the procedure needs to be completed. NYHA, New York Heart Association; ECG, electrocardiogram; UCG, ultrasound cardiogram; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro b-type natriuretic peptide; FBG, fasting blood glucose; HBA1c, hemoglobin A1c; OCT, optical coherence tomography; SAQ, Seattle Angina Pectoris Questionnaire; SF-36, Short-From-36 Health Survey; PHQ-9, Patient Health Questionnie-9; GAD-7, Generalized Anxiety Disorder Questionnie-7; MMAS-8, 8-item Morisky Medication Adherence Scale; MACE, major adverse cardiac event.

Table 4 Data collection

Content	Information
Demographics	Age, gender, contact information, education level, occupation, marital status and diet
Medical histories	MI, hypertension, diabetes, hyperlipidemia, stroke, peripheral vascular disease, renal failure, obstructive sleep apnea, cancer, coronary revascularization, smoking, drinking and family history
Medications	Aspirin, P2Y12 receptor inhibitors, statins, other lipid-lowering drugs, nitrates, β-blockers, antihypertensive drugs and hypoglycemic drugs
Admission conditions	Symptoms, blood pressure, heart rate, BMI, diagnosis, cardiac function, ECG, SAQ, PHQ-9, GAD-7 and SF-36
Laboratory results	Routine blood tests, coagulation function, platelet function tests, FBG, HBA1c, ALT, AST, hsCRP, BNP, CK-MB, TC, TG, HDL-C, LDL-C, LVEF (UCG), troponin, creatinine
Coronary angiography	SYNTAX score; LM lesion; number of vascular lesions; PCI/CABG; CAG time
OCT imaging results	FCT, minimum lumen area, overall macrophage accumulation grade, lipid index, mean lipid arc
Endothelial function tests	RHI
Clinical events	MACE, adverse drug reactions

MI, myocardial infarction; BMI, body mass index; ECG, electrocardiogram; SAQ, Seattle Angina Pectoris Questionnaire; PHQ-9, Patient Health Questionnie-9; GAD-7, Generalized Anxiety Disorder Questionnie-7; SF-36, Short-From-36 Health Survey; FBG, fasting blood glucose; HBA1c, hemoglobin A1c; ALT, alanine aminotransferase; AST, aspartate aminotransferase; hsCRP, hypersensitive C-reactive protein; BNP, B-Type Natriuretic Peptide; CK-MB, creatine kinase-MB; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; UCG, ultrasound cardiogram; LM, left main; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CAG, coronary angiography; OCT, optical coherence tomography; FCT, fibrous cap thickness; RHI, reactive hyperemia index; MACE, major adverse cardiac event.

measurements, LDL-C, and endothelial function on MACE will be analyzed using Cox proportional hazard regression models. Missing data will be processed by multiple imputation. Primary analyses will be based on the intention to treat (ITT) principle, that including all randomized participants, regardless of protocol adherence, to minimize bias and maintain the integrity of randomization. A sensitivity analysis for patients with missing data will be conducted and baseline characteristics will be compared with those of patients with complete data. Statistical analysis will be performed by IBM SPSS Statistics 23.0. $P<0.05$ will be considered statistically significant.

Enrollment strategy

It is anticipated that 240 participants will be enrolled over a 36-month period, with an expected recruitment rate of approximately 7 participants per month. To encourage participation, researchers will offer non-financial incentives, such as educational materials about cardiovascular health, which will be provided to participants.

Discussion

To date, the study populations using intravascular imaging to assess the effect of PCSK9i have been mostly differentiated according to the clinical manifestations of CAD. There is a gap in the study of specific populations at risk for ASCVD. HUYGENS and PACMAN-AMI studies focused on patients with acute myocardial infarction (AMI), with early PCSK9i intervention in the experimental groups, demonstrating the stabilizing effect of PCSK9i on coronary plaques in non-infarct-related arteries (18,38). Previous guidelines have generally assessed the 10-year overall risk of cardiovascular events in patients, categorizing them into different risk groups. However, even among ASCVD patients, the risk of recurrent ASCVD events varies significantly. The 10-year recurrence rate of major vascular events is approximately 17%, with 18% of patients having a recurrence rate of less than 10%, and 22% having a rate exceeding 30% (39). Stratifying ASCVD patients according to their risk of recurrent cardiovascular events is crucial for guiding secondary prevention in this population. Therefore, the inclusion of patients with very high-risk ASCVD in this experiment is an innovation. Secondly, most of the intravascular imaging studies assessing the effects of PCSK9i have been currently conducted in European and American populations. Among them, 9 OCT studies were conducted in Asian populations with medium-intensity statin management, and only 3 were combined with PCSK9i, with the longest

follow-up time of 9 months (40-42). However, long-term follow-up studies of high-intensity statin combined with PCSK9i in Asian populations are still lacking, thus the treatment regimen design of this experiment is another innovation. In this study, the changes in plaque vulnerability will be detected by OCT. OCT can be used to accurately and quantitatively assess plaque vulnerability characteristics *in vivo*, and FCT is a major determinant of plaque vulnerability. Therefore, observing changes in FCT of TCFA by OCT is more likely to reveal changes in plaque vulnerability, thereby reducing the rate of MACE. Previous studies indicated that FMD and reactive hyperemia-peripheral arterial tonometry (RH-PAT) had similar predictive values for future cardiovascular events (43). RH-PAT is semi-automated, easier to operate than FMD, and provides better inter-observer reproducibility (44). Therefore, using RH-PAT technology to assess the impact of PCSK9i on endothelial function in patients with very high-risk ASCVD is another innovative aspect of this study.

However, there are some limitations to this study. This is an investigator-initiated trial. Considering the feasibility of conducting both OCT and endo-PAT and the consistency of investigator evaluations, we will conduct a single-center randomized controlled study rather than a multicenter study. In addition, due to the lack of OCT imaging fusion module in our center, OCT plaque recognition will be based on the relative distance to the characteristic lumen structures (such as bifurcations, calcifications, etc.), and the quality control will be carried out by experienced OCT technicians and surgeons to reduce the error of plaque location and measurement.

To address the limitations of a single-center design, we may further consider establishing collaborations with other eligible and intentional centers for data sharing and post-trial meta-analysis, which can enhance the generalizability of the study findings. Additionally, external blinded reviews of the imaging data could provide further robustness. For the limitations in OCT imaging, engaging multiple independent experienced technicians to analyze the images can help mitigate the challenges related to plaque location and measurement accuracy. To enhance patient compliance in follow-up, an electronic reminder system or telemedicine tools could be employed to ensure consistent follow-up throughout the study duration.

Acknowledgments

The authors would like to thank ProoFine English Studio for their help in polishing our manuscript.
Funding: This study is supported by the project of Capital Health Development Research Project (No. 2024-2-2069), China International Medical Foundation (Grant 2022-N-01-01), Beijing Lab for Cardiovascular Precision Medicine (Grant PXM2020_014226_000017_00377132_FCG) and Beijing Engineering Research Center of Cardiovascular Wisdom Diagnosis and Treatment. These funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-336/rc

Peer Review File: Available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-336/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cdt.amegroups.com/article/view/10.21037/cdt-24-336/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study has received approval from the Ethics Committee of Beijing Anzhen Hospital Medical (No. ks202002), which will be conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was registed at Chinese Clinical Trial Registry [ChiCTR, chictr.org.cn (ChiCTR2000032570)]. Informed consent will be obtained from all participants.

References

1. Joint COTC. Chinese guidelines for lipid management (2023). Chinese Journal of Cardiology 2023;51:221-55.
2. Zeng YY, Liu J, Hao YC, et al. The expanding needs on lipid-lowering treatment in patients with acute coronary syndrome by applying newly issued definition of extreme high-risk by Chinese Society of Cardiology. Chinese Journal of Cardiology 2020;48:1039-46.
3. Cardiology AACH, Cardiology. EBOC. Chinese expert consensus on lipid management of very high-risk atherosclerotic cardiovascular disease patients. Chinese Journal of Cardiology 2020;48:280-6.
4. Cholesterol Treatment Trialists' (CTT) Collaboration; Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010;376:1670-81.
5. Mitani H, Suzuki K, Ako J, et al. Achievement Rates for Low-Density Lipoprotein Cholesterol Goals in Patients at High Risk of Atherosclerotic Cardiovascular Disease in a Real-World Setting in Japan. J Atheroscler Thromb 2023;30:1622-34.
6. Ng AK, Ng PY, Ip A, et al. High-Intensity Statin vs. Low-Density Lipoprotein Cholesterol Target for Patients Undergoing Percutaneous Coronary Intervention: Insights From a Territory-Wide Cohort Study in Hong Kong. Front Cardiovasc Med 2021;8:760926.
7. Kim J, Park KT, Jang MJ, et al. High-Intensity Versus Non-High-Intensity Statins in Patients Achieving Low-Density Lipoprotein Cholesterol Goal After Percutaneous Coronary Intervention. J Am Heart Assoc 2018;7:e009517.
8. Xu S, Ilyas I, Little PJ, et al. Endothelial Dysfunction in Atherosclerotic Cardiovascular Diseases and Beyond: From Mechanism to Pharmacotherapies. Pharmacol Rev 2021;73:924-67.
9. Bu F, Wang J, Chen J, et al. HCC-1 Accelerates Atherosclerosis by Inducing Endothelial Cell and Macrophage Pyroptosis and Serves as an Early Diagnostic Biomarker. Arterioscler Thromb Vasc Biol 2024;44:2088-107.
10. Horikoshi T, Nakamura T, Yamada R, et al. Association between carotid plaque progression and persistent endothelial dysfunction in an infarct-related coronary artery in STEMI survivors. Heart Vessels 2024. [Epub ahead of print]. doi: 10.1007/s00380-024-02444-z.
11. Godo S, Corban MT, Toya T, et al. Association of coronary microvascular endothelial dysfunction with vulnerable plaque characteristics in early coronary atherosclerosis. EuroIntervention 2020;16:387-94.
12. Gaba P, Gersh BJ, Muller J, et al. Evolving concepts of the vulnerable atherosclerotic plaque and the vulnerable patient: implications for patient care and future research. Nat Rev Cardiol 2023;20:181-96.
13. Kume T, Akasaka T, Kawamoto T, et al. Measurement of the thickness of the fibrous cap by optical coherence tomography. Am Heart J 2006;152:755.e1-4.
14. Aguirre AD, Arbab-Zadeh A, Soeda T, et al. Optical Coherence Tomography of Plaque Vulnerability and Rupture: JACC Focus Seminar Part 1/3. J Am Coll Cardiol 2021;78:1257-65.
15. Mu G, Xiang Q, Zhou S, et al. Efficacy and Safety of PCSK9 Monoclonal Antibodies in Patients at High Cardiovascular Risk: An Updated Systematic Review and Meta-Analysis of 32 Randomized Controlled Trials. Adv Ther 2020;37:1496-521.
16. Barbieri L, Tumminello G, Fichtner I, et al. PCSK9 and Coronary Artery Plaque-New Opportunity or Red Herring? Curr Atheroscler Rep 2024;26:589-602.
17. Pérez de Isla L, Díaz-Díaz JL, Romero MJ, et al. Characteristics of Coronary Atherosclerosis Related to Plaque Burden Regression During Treatment With Alirocumab: The ARCHITECT Study. Circ Cardiovasc Imaging 2024;17:e016206.
18. Räber L, Ueki Y, Otsuka T, et al. Effect of Alirocumab Added to High-Intensity Statin Therapy on Coronary Atherosclerosis in Patients With Acute Myocardial Infarction: The PACMAN-AMI Randomized Clinical Trial. JAMA 2022;327:1771-81.
19. Biccirè FG, Häner J, Losdat S, et al. Concomitant Coronary Atheroma Regression and Stabilization in Response to Lipid-Lowering Therapy. J Am Coll Cardiol 2023;82:1737-47.
20. Ferri N, Marchianò S, Tibolla G, et al. PCSK9 knock-out mice are protected from neointimal formation in response to perivascular carotid collar placement. Atherosclerosis 2016;253:214-24.
21. Yang J, Ma X, Niu D, et al. PCSK9 inhibitors suppress oxidative stress and inflammation in atherosclerotic development by promoting macrophage autophagy. Am J Transl Res 2023;15:5129-44.
22. Shin D, Kim S, Lee H, et al. PCSK9 stimulates Syk, PKCδ, and NF-κB, leading to atherosclerosis progression independently of LDL receptor. Nat Commun 2024;15:2789.
23. Waltmann MD, Basford JE, Konaniah ES, et al. Apolipoprotein E receptor-2 deficiency enhances

macrophage susceptibility to lipid accumulation and cell death to augment atherosclerotic plaque progression and necrosis. Biochim Biophys Acta 2014;1842:1395-405.
24. Marfella R, Prattichizzo F, Sardu C, et al. Evidence of an anti-inflammatory effect of PCSK9 inhibitors within the human atherosclerotic plaque. Atherosclerosis 2023;378:117180.
25. Antonopoulos AS, Angelopoulos A, Papanikolaou P, et al. Biomarkers of Vascular Inflammation for Cardiovascular Risk Prognostication: A Meta-Analysis. JACC Cardiovasc Imaging 2022;15:460-71.
26. Everett BM. Residual Inflammatory Risk: A Common and Important Risk Factor for Recurrent Cardiovascular Events. J Am Coll Cardiol 2019;73:2410-2.
27. Rexhaj E, Bär S, Soria R, et al. Effects of alirocumab on endothelial function and coronary atherosclerosis in myocardial infarction: A PACMAN-AMI randomized clinical trial substudy. Atherosclerosis 2024;392:117504.
28. Xu L, Wang Y, Wang Y, et al. Early Use of PCSK9 Inhibitors in the Prognosis of Patients with Acute Coronary Syndrome by Protecting Vascular Endothelial Function. Pharmacology 2024. [Epub ahead of print]. doi: 10.1159/000540083.
29. Usui E, Hanyu Y, Sakamoto T, et al. Association between optical coherence tomography-defined culprit morphologies and changes in hyperemic coronary flow after elective stenting assessed by transthoracic Doppler echocardiography. PLoS One 2024;19:e0307384.
30. Tufaro V, Jaffer FA, Serruys PW, et al. Emerging Hybrid Intracoronary Imaging Technologies and Their Applications in Clinical Practice and Research. JACC Cardiovasc Interv 2024;17:1963-79.
31. Mézquita AJV, Biavati F, Falk V, et al. Clinical quantitative coronary artery stenosis and coronary atherosclerosis imaging: a Consensus Statement from the Quantitative Cardiovascular Imaging Study Group. Nat Rev Cardiol 2023;20:696-714.
32. Jiang S, Fang C, Xu X, et al. Identification of High-Risk Coronary Lesions by 3-Vessel Optical Coherence Tomography. J Am Coll Cardiol 2023;81:1217-30.
33. Masarone M, Motta BM, Torre P, et al. Evaluating cardiovascular risk in metabolic steatosis with precision medicine non-invasive approaches: insights from a cohort study. Intern Emerg Med 2024;19:2293-307.
34. Fatihoglu SG, Jam F, Okutucu S, et al. Noninvasive Investigation of the Presence and Extent of Coronary Artery Disease by the Evaluation of Fingertip-Reactive Hyperemia. Med Princ Pract 2022;31:262-8.
35. Chan AW, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200-7.
36. Axtell AL, Gomari FA, Cooke JP. Assessing endothelial vasodilator function with the Endo-PAT 2000. J Vis Exp 2010;2167.
37. Allan RB, Delaney CL, Miller MD, et al. A comparison of flow-mediated dilatation and peripheral artery tonometry for measurement of endothelial function in healthy individuals and patients with peripheral arterial disease. Eur J Vasc Endovasc Surg 2013;45:263-9.
38. Nicholls SJ, Kataoka Y, Nissen SE, et al. Effect of Evolocumab on Coronary Plaque Phenotype and Burden in Statin-Treated Patients Following Myocardial Infarction. JACC Cardiovasc Imaging 2022;15:1308-21.
39. Kaasenbrood L, Boekholdt SM, van der Graaf Y, et al. Distribution of Estimated 10-Year Risk of Recurrent Vascular Events and Residual Risk in a Secondary Prevention Population. Circulation 2016;134:1419-29.
40. Yano H, Horinaka S, Ishimitsu T. Effect of evolocumab therapy on coronary fibrous cap thickness assessed by optical coherence tomography in patients with acute coronary syndrome. J Cardiol 2020;75:289-95.
41. Sugizaki Y, Otake H, Kawamori H, et al. Adding Alirocumab to Rosuvastatin Helps Reduce the Vulnerability of Thin-Cap Fibroatheroma: An ALTAIR Trial Report. JACC Cardiovasc Imaging 2020;13:1452-4.
42. Gao F, Wang ZJ, Ma XT, et al. Effect of alirocumab on coronary plaque in patients with coronary artery disease assessed by optical coherence tomography. Lipids Health Dis 2021;20:106.
43. Matsuzawa Y, Kwon TG, Lennon RJ, et al. Prognostic Value of Flow-Mediated Vasodilation in Brachial Artery and Fingertip Artery for Cardiovascular Events: A Systematic Review and Meta-Analysis. J Am Heart Assoc 2015;4:e002270.
44. McCrea CE, Skulas-Ray AC, Chow M, et al. Test-retest reliability of pulse amplitude tonometry measures of vascular endothelial function: implications for clinical trial design. Vasc Med 2012;17:29-36.

Cite this article as: Gao B, Nan N, Zhang M, Tian J, Ren Y, Xue Y, Zhang M, Song X, Ge C. Assessing the impact of evolocumab on thin-cap fibroatheroma and endothelial function in patients with very high-risk atherosclerotic cardiovascular disease: a study protocol for a randomized controlled trial. Cardiovasc Diagn Ther 2024;14(6):1236-1246. doi: 10.21037/cdt-24-336

