A Randomized Controlled Trial of Intensive Lipid-Lowering Therapy to Improve Prognosis in Patients with Acute Coronary Syndrome and Establishment of A Model for Evaluating Risk for Residual Serum Lipid

-- A Randomized Controlled Trial of Early Initiation of Intensive Lipid-Lowering Therapy for Patients with Acute Coronary Syndrome undergoing Percutaneous Coronary Intervention

Research protocol

Version Number: V2.0

Version Date: 20230705

Project source: Chinese Academy of Medical Sciences

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Project implementation period: December 2023 to December 2025

Contents

1. Research background

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death worldwide, and its incidence is increasing yearly in China, which has not yet reached the inflection point [1]. Acute coronary syndrome (ACS) is a severe form of ASCVD, and lipid-lowering and antithrombotic therapy are the two core therapies. In the latest ESC/EAS guidelines for lipid management [2], for ACS patients, the target LDL-C is <1.4 mmol/L and ≥50% reduction from baseline, and specific initiatives to achieve this target are proposed, emphasizing the timing of clinical application and status of the novel lipid-lowering agent-proprotein convertase subtilisin/kexin type 9 monoclonal antibody (PCSK9) (hereafter referred to as PCSK9 antibody). In recent years, large-scale randomized controlled trials and outcomes of PCSK9 antibodies have demonstrated that PCSK9 antibodies further reduce adverse cardiovascular events by significantly lowering LDL-C levels under the background statin (± cholesterol absorption inhibitor) therapy [3-5]. The introduction of PCSK9 antibodies allowed for the reduction of LDL-C to unprecedented levels. From the "cholesterol principle" perspective, it is theoretically reasonable to add a PCSK9 inhibitor to statins as soon as possible during hospitalization for ACS patients. Still, there is no clear evidence from large RCTs. Current evidence supports that for ACS patients, PCSK9 antibodies could be used only when LDL-C is still not up to standard based on treatment with the maximum tolerable dose of statins during the first 2-3 months. However, the immediate initiation of PCSK9 antibodies during the acute phase of ACS (before hospital discharge) has yet to be studied.

1.1 Evidence-based evidence of cardiovascular benefit from early initiation of intensive lipid-lowering for ACS patients

Previous statins-related studies have found that the MIRACL study (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) initiated treatment with atorvastatin 80 mg/day or placebo **four days after hospitalization in 3,086 patients with ACS for four months** [6]. **Mean LDL-C at four months** were 72 and 135 mg/dl, respectively, and the incidence of MACE was 14.8% and 17.4% (RR, 0.84; 95% CI, 0.70-1.00; P=0.048)[7]. The PROVE-IT trial (Pravastatin or Atorvastatin Evaluation and Infection Therapy) compared **4,162** patients with ACS after ten days with atorvastatin 80 mg/day and pravastatin 40 mg/day given for a median duration of two years, with a median LDL-C of 62 mg/dl and 95 mg/dl, respectively [8]. In the early benefit analysis in the PROVE-IT trial, **the incidence of MACE was lower in the early initiation of atorvastatin 80 mg group after ACS,** with a 30-day post-randomization group primary endpoint (3.0% vs. 4.2%; **HR, 0.72;** 95% CI, 0.52-0.99; P=0.046) and triple primary composite endpoint -defined as death, myocardial infarction, or recurrent ACS with rehospitalization (9.6% vs. 13.1%; **HR,**

0.72; 95%CI, 0.58-0.89; P=0.003) was significantly different between groups. Besides, the four months primary composite endpoint was different between groups (8.2% vs. 10.2%; HR, 0.81; 95 CI%, 0.65-0.98; P=0.03) [9]. The above findings suggest that **in the statin times, compared with conventional lipid-lowering therapy, early treatment (Days 4-10 after ACS) with intensive lipid-lowering (high-intensity statins) has more clear cardiovascular benefits, which appear as early as the 30th day and most significantly at four months for ACS patients.**

1.2 Evidence-based evidence of more cardiovascular benefit in ACS patients by achieving lower LDL-C

A recent meta-analysis that included 19 studies (15 for statins, 3 for PCSK9 antibodies, and 1 for ezetimibe, n=152,507) comparing intensive lipid-lowering (n=76,679) with conventional lipid-lowering (n=75,829) found that **intensive LDL-C-lowering further reduced adverse cardiovascular events** (RR, 0.81; 95% CI, 0.77-0.86) [10]. Evidence indicated that most ACS patients can achieve very low LDL-C to **less than 1.0 mmol /L** with PCSK9 antibodies in combination with statin ± ezetimibe, which has confirmed safety. Among these studies, the FOURIER study, as well as the ODESSEY OUTCOME study, have confirmed that in ACS patients with sub-standard LDL-C, the addition of PCSK9 antibodies results in lower LDL-C levels, which leads to more cardiovascular benefits and a lower incidence of MACE [3-5]. The latest study, FOURIER-OLE (open-label extension), suggested that ASCVD patients applied evolocumab for up to 8.4 years (median five years), with a median LDL-C level of 30 mg/dL. Still, the incidence of adverse events such as serious adverse events, muscle-related events, new-onset diabetes mellitus, hemorrhagic strokes, and neurocognitive events was not increased by long-term use of evolocumab compared with the placebo group. Besides, long-term maintenance of <20 mg/dl (<0.5 mmol/L) by evolocumab was associated with a lower risk of cardiovascular outcomes [11-12]. The ODSSEY OUTCOME study found a trend toward a decrease in all-cause deaths in the Alirocumab group, with a four months LDL-C of up to 30 mg/dl (linear trend-adjusted P=0.017) [13]. The evidence from the above studies confirmed that **lower LDL-C levels resulted in more cardiovascular benefits without increasing the incidence of additional adverse events.**

1.3 Delayed benefitss and memory effects of applying intensive lipid-lowering therapy in ACS patients

The delayed benefits, or memory effects of intensive lipid-lowering therapy have been defined as the benefit obtained after a specific duration of intensive lipid-lowering treatment has been applied that persists for a more extended period after the cessation of the trial (discontinuation of the medication) to examine the long-term clinical benefits of the pharmacologic intervention. The memory effect of intensive

statins therapy has been demonstrated. A systematic review studying the legacy effects of treating hypertriglyceridemia included 13 RCTs of lipid-lowering drugs compared with placebo or conventional lipid-lowering therapy with follow-up at the end of the trial. All of these demonstrated that lipid-lowering therapy produces a legacy effect of preventing both fatal and nonfatal events, which showed that early treatment leads to more profound clinical effects [14]. The 20-year follow-up of the WOSCOPS trial about the memory effect of statins therapy has confirmed [15] that compared with the control group, the cardiovascular risk-benefit for five years of lipid-lowering therapy with pravastatin application persisted for 20 years. These benefits were also evident across outcomes (mortality and hospitalization) and did not diminish over time. However, previous studies of memory effects have not indicated whether these benefits were unique to intensive statin therapy or due to statin lowering serum lipid profile levels. In a post hoc analysis of the ODYSSEY OUTCOMES trial comparing the efficacy of a PCSK9 inhibitor (alirocumab) to placebo, both groups were used for high-intensity or maximally tolerated doses of statin therapy. Patients with two consecutive LDL-C levels <0.39 mmol/L (15 mg/dL) on alirocumab, then alirocumab was discontinued. Over a median follow-up of 2.8 years, the incidence of MACE in alirocumab group that reached the target LDL-C was significantly lower than that in placebo group (6.4% vs. 8.4%; **HR, 0.72**; 95% CI, 0.51-0.997; *P*=0.047). These suggested that after the use of intensive lipid-lowering therapy (statin + alirocumab) to achieve limited duration with an LDL-C level of <0.39 mmol /L, followed by statin monotherapy was associated with a lower risk of MACE compared with statin monotherapy. This clinical benefit persisted for several years after discontinuation of PCSK9 inhibitors [16].

1.4 PCSK9 and platelet functions

In vitro studies, in vivo animal studies, and human studies have confirmed that PCSK9 levels correlate with platelet reactivity [17-20]. One study found that plasma levels of sP-selectin, a biomarker of platelet and endothelial activation, was significantly lower in PCSK9-/- mice than in control mice, suggesting that platelet function is impaired in PCSK9-/- mice [17]. Increases in thrombotic events of relevance have been detected in mice transfected with the PCSK9 adenovirus, and human studies have confirmed a positive correlation between PCSK9 levels and platelet reactivity [20].

A prospective observational study consecutively enrolled ACS patients receiving prasugrel or ticagrelor and undergoing PCI [21] used a multiplate analyzer to determine adenosine diphosphate (ADP)-induced platelet aggregation. Major adverse cardiovascular events (MACE) were defined as a composite of cardiovascular death, myocardial infarction, unstable angina, stent thrombosis, repeat

revascularization, and ischemic stroke with a 12-month follow-up. A direct association was found between elevated PCSK9 serum levels and platelet reactivity (r=0.30; p=0.004). Platelet reactivity was assessed according to tertiles of PCSK9 levels and was found to be significantly higher in those located in the highest tertile than in the lowest tertile (p=0.02). In patients with PCSK9 levels located in the highest tertile, 13/59 (22.03%) developed MACE within one year, whereas in the lowest tertile of PCSK9, 2/59 (3.39%) did so. At one-year follow-up, PCSK9 was independently associated with an increase in ischemic MACE: the risk ratio for the occurrence of MACE at high PCSK9 levels versus low PCSK9 levels was 2.62%. The risk ratio for the occurrence of MACE was 2.62 (95% CI 1.24-5.52; p = 0.01).

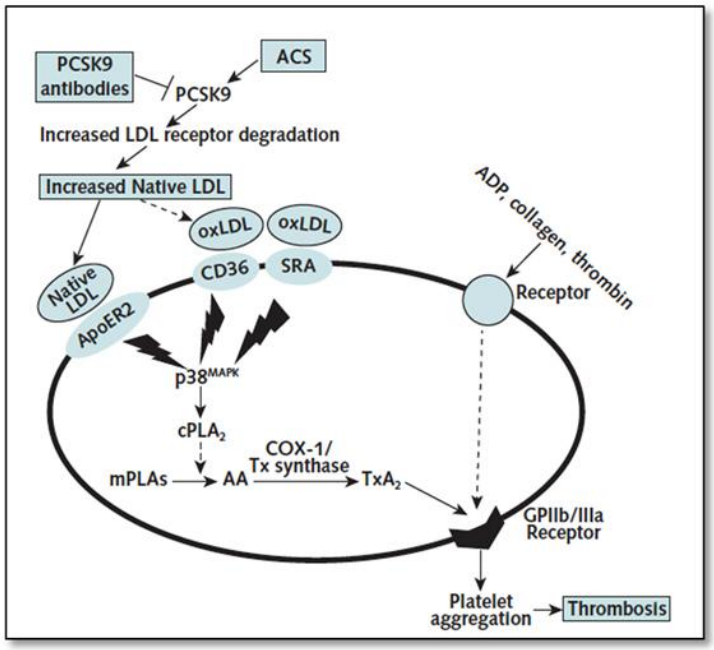

Figure 1 Cited in Navarese EP, Kolodziejczak M, Kereiakes DJ, Tantry US, O'Connor C, Gurbel PA. Proprotein Convertase Subtilisin/Kexin Type 9 Monoclonal Antibodies for Acute Coronary Syndrome: a Narrative Review. annals of internal medicine 2016;164:600-7.

Plasma PCSK9 levels are elevated in the acute phase in ACS patients. Evidence confirms that elevated PCSK9 levels are associated with atherosclerotic plaque instability, inflammatory response, and platelet reactivity [22-23].

PCSK9 inhibitors can potentially deplete cholesterol from platelet membranes by significantly reducing LDL-C levels; its inhibitory effect on platelet activation may also be mediated by decreasing the ability of platelets to oxidize LDL, thereby decreasing the latter's ability to stimulate platelet activity via the CD36 and LOX- 1 receptor pathways; in addition, PCSK9 inhibitors reduce levels of lipoprotein(a) [Lp(a)] (a primary carrier of oxidized phospholipids), thereby potentially impairing its ability to activate platelets via toll-like receptor 2 (TRL2); PCSK9 inhibitors also increase high-density lipoprotein (HDL), reduce platelet activation acting on apoER2

and SRB1 receptors, and remove cholesterol from platelet membranes. By both intracellular and extracellular mechanisms, PCSK9 inhibitors enhance the hepatic LDLR expression and possibly LRP-1 expression, potentially enhancing FVIII internalization and degradation and reducing FVIII plasma levels. In addition, PCSK9 inhibitors may also reduce the activity of circulating tissue factor (TF) by accelerating its clearance.

Several studies have shown that PCSK9 antibodies' application in ACS patients significantly reduced major adverse cardiovascular events (MACE) in post-ACS patients by plaque modification, interfering with lipid metabolism, platelet aggregation and ultimately improving endothelial function [24-25]. Therefore, this may justify **earlier initiation of** PCSK9 monotherapy.

1.5 Evidence that early initiation of intensive lipid-lowering with PCSK9i results in earlier achievement of lower LDL-C levels

The risk of major adverse cardiovascular events in the first year after ACS is very high. Early initiation of PCSK9 monotherapy after ACS reduces the incidence of MACE. In the newly completed EVACS (Evolocumab in Acute Coronary Syndrome) study, Evolocumab resulted in 90% of patients with LDL-C < 55 mg/dL compared to 11% of patients receiving statins only [26]. In the EVOPACS study (Evolocumab for Early Reduction of LDL-cholesterol Levels in Patients With Acute Coronary Syndromes), Evolocumab resulted in 95.7% of patients achieving LDL-C levels < 55 mg/dL [27].

Taking the **above evidence** into account **(Figure 2)**, we **hypothesize that** the early initiation of lipid-lowering therapy including PCSK9 antibodies for **ACS** patients undergoing PCI **as soon as possible** to achieve lower LDL-C levels, is predicted to reduce the incidence of major adverse cardiovascular events in patients after discontinuation of the drug compared with the conventional lipid-lowering therapy. Thus we propose the optimization strategy of "intensive lipid-lowering with PCSK9 antibodies can **be initiated as early as possible** in ACS patients undergoing PCI.

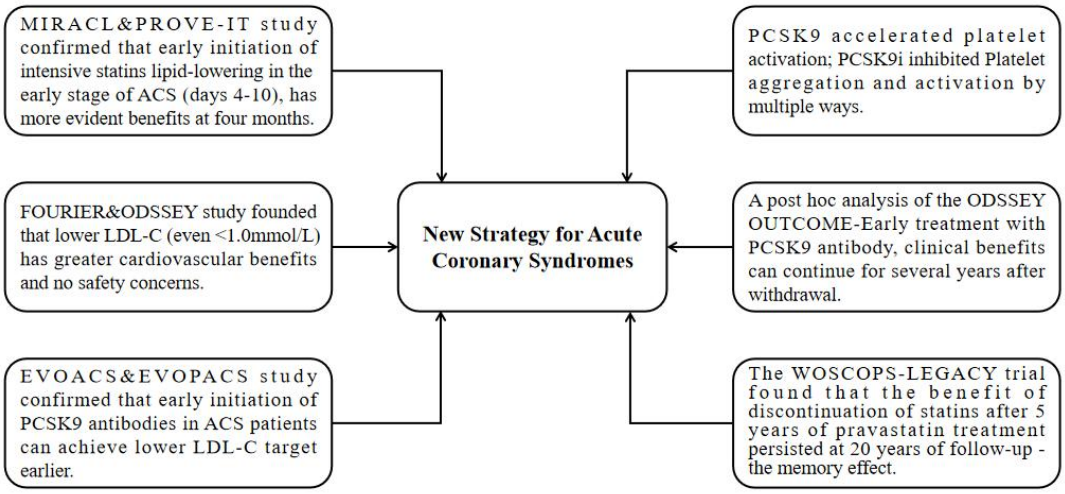

Figure 2 Evidence supporting the New Strategy for Acute Coronary Syndromes

2. Research purpose

In ACS patients undergoing PCI, early initiation of intensive lipid-lowering with PCSK9 antibodies, namely achieving lower LDL-C levels as soon as possible, is expected to reduce the incidence of major adverse cardiovascular events in patients after discontinuation of the drug compared with conventional lipid-lowering therapy. Therefore, an optimization strategy of "early initiation of intensive lipid-lowering with PCSK9 antibodies in ACS patients undergoing PCI " is proposed.

3. Research method

3.1 Research design method

This is a national, multicenter, randomized controlled study with Fu Wai Hospital as the group leader and at least 7 sub-centers. Patients eligible for enrollment will be randomized into: group 1 (G1, experimental group): intensive lipid-lowering (statins + PCSK9 antibodies); group 2 (G2, control group) conventional lipid-lowering (statins + cholesterol absorption inhibitor).

Methods of randomization: All eligible patients entering the appropriate group are randomly grouped using IRT to obtain a random number, which is automatically assigned to a random number by the system. The planned time to complete enrollment of all patients was at most one year, with a maximum follow-up of two years. Safety assessments included monitoring of all adverse events (AEs), serious adverse events (SAEs), and regular monitoring of vital signs and clinical laboratory tests.

3.2 Research object

3.2.1 Criteria for inclusion, exclusion, and withdrawal

A total of 3684 patients will be enrolled. **Inclusion criteria:** Patients 18 to 75 years of age with acute non-ST elevation myocardial infarction (NSTEMI), completing PCI and 1.8mmol/L< Baseline LDL-C level <3.4mmol/L. NSTE-ACS includes non-ST-segment elevation myocardial infarction and unstable angina. **Exclusion criteria:** 1) Severe heart failure (Killip class III or IV) or cardiogenic shock; 2) Known hemorrhagic stroke at any time; 3) Uncontrolled or recurrent arrhythmic events; 4) Uncontrolled hypertension; 5)Severe hepatic and renal dysfunction, or CK >5 times the ULN; 6) Malignant tumor; 7) Intolerant to statins or cholesterol absorption inhibitor; 8) Intolerant to injections; 9) Life expectancy < 1 year; 10) Poor compliance. **Withdrawal criteria:** Patients may withdraw from the study at any time.

3.2.2 Grouping of research subjects

Randomization: 1842 cases in each group. Group 1 (G1, experimental group, n=1842): intensive lipid-lowering (statin + PCSK9 antibodies). Group 2 (G2, control group, n=1842): conventional lipid-lowering (statin + cholesterol absorption inhibitor). The PCSK9 antibodies in this study are toleucizumab 150 mg q2w i.h. In terms of lipid-lowering therapy for both groups, lipid-related guidelines are followed to ensure that, as far as possible, lipid-lowering therapy other than PCSK9 antibodies remained unchanged throughout the study period, provided that no serious safety issues occurred. In terms of lipid compliance, the baseline LDL-C range of 1.8-3.4 mmol/L in the enrollment criteria has excluded the population with high baseline LDL-C levels that are not easy to comply with, and lipid-lowering drugs other than PCSK9 antibodies can satisfy the guideline requirement of LDL-C compliance level. In addition, concerning the ODYSSEY OUTCOMES study, LDL-C <0.4 mmol/L (15 mg/dL) was selected as the safety threshold (discontinuation criterion) for the application of PCSK9 monoclonal antibody to achieve very low levels of LDL-C [16].

SCREENING PERIOD: patients 18 to 75 years of age with acute non-ST elevation myocardial infarction (NSTEMI), completing PCI and 1.8mmol/L< Baseline LDL-C level <3.4mmol/L will be screened at each subcenter.

Random Grouping: All eligible patients are grouped using randomization, and the system generates a random list, automatically assigning patient numbers to random numbers.

BLINDED AND UNBLINDED: This study utilized an unblinded design. Enrolled patients, researchers, academic research center staff, and treating physicians know the treatment.

Visit 0 (V0): is the day of enrollment. Patients will sign informed consent. We will complete all baseline data collection and give appropriate treatment therapy according to groups.

Visit 1 (V1): is the day at the end of 1 month after enrollment. We use routine laboratory tests to determine the patients' tolerance of the treatment therapy (safety assessment).

Visit 2 (V2): is the day at the end of 6 months after enrollment. We use blood for routine laboratory tests, record major adverse cardiovascular events (MACEs), and follow patients' tolerance (safety assessment) and compliance with the therapy.

Visit 3 (V3): is the day at the end of year 1 after enrollment. We use blood for routine laboratory tests, record the secondary key observational endpoint (the occurrence of major adverse cardiovascular and cerebrovascular events (MACCE) at the end of year 1), and follow up on the patients' tolerance (safety assessment) and compliance with the therapy.

Visit 4 (V4): is the day at the end of year 2 after enrollment. We use blood for routine laboratory tests and record the primary observation endpoint (the occurrence of MACCE at the end of year 2).

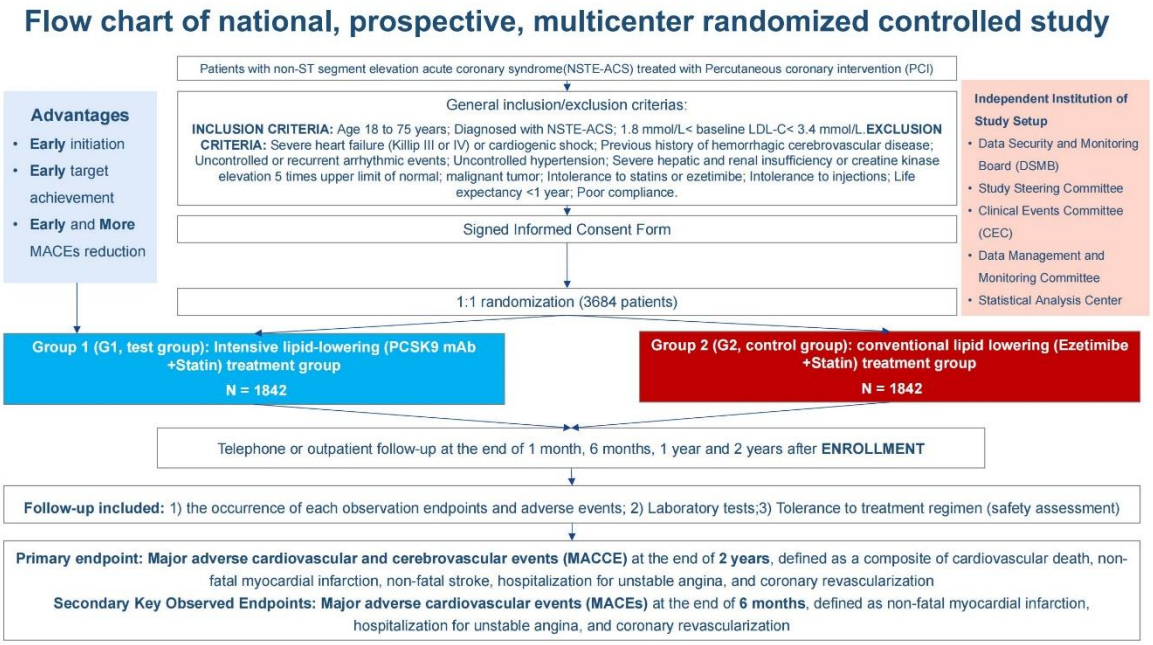

Figure 3: Flow chart of the study

3.3 Selection and validation of study or outcome indicators

Primary Observational Endpoint: The primary observational endpoint is 2-year MACCE (Major adverse cardiovascular and cerebrovascular events, including cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, and coronary revascularization). Coronary revascularization included undergoing coronary intervention (PCI) and coronary artery bypass grafting (CABG).

Secondary key observational endpoints: Key secondary observational endpoints include MACEs (major adverse cardiovascular events, defined as cardiovascular death, nonfatal myocardial infarction, hospitalization for unstable angina, and coronary revascularization) at the end of 2 years.

Secondary Observational Endpoints: Secondary observational endpoints include MACCE at the end of 1 year (Major adverse cardiovascular and cerebrovascular events, defined as cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, coronary revascularization, and bleeding-related events)

Additional Observational Endpoints: Additional observational endpoints include the individual observational endpoints that make up the MACCE at the end of 2 years.

3.4 Early termination of study

Early termination of the study means terminating the study due to efficacy or safety. If safety concerns pose unexpected risks to patients, the study may be suspended or terminated early when necessary. Suppose this study is brought up for termination. In that case, the Clinical Coordinating Center will provide a written statement to the Collaborative Principal Investigators, so that each Collaborative Principal Investigator can notify their respective Ethics Committees and patients. The Clinical Coordinating Center will also notify the appropriate authorities. The Clinical Coordinating Center may terminate the enrollment of the Collaboration or may no longer allow the Investigator or Collaboration to participate in the study if there is evidence that the Investigator has failed to conduct appropriate clinical standards or has failed to comply with the study protocol. Notification of suspension or termination of the study or the study collaborative's/investigator's participation in the study will be sent to the investigator and the Ethics Committee. Once the study is terminated early, patients will be notified according to the process and receive a routine lipid-lowering regimen established by the clinician.

4.Sample size estimation

Refer to previous studies, the application of PCSK9 antibodies based on statin therapy significantly reduced the incidence of MACEs (defined as coronary heart disease death, non-fatal infarction, re-hospitalization for unstable angina, or ischemic stroke events) compared with placebo (OR=0.72) [16], and this benefit was more evident in the high-risk ASCVD population. Evidence from previous studies suggests [5] that the 2-year event rate of MACEs (definition: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization) in the control group (G2, conventional lipid-lowering) was approximately 13.6%, presupposing that the OR of the intensive lipid-lowering group with early initiation of PCSK9i in the present study relative to that of the conventional lipid-lowering group = 0.70, and the 2-year MACEs (defined as: cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, and coronary revascularization) event rate in the test group (G1, intensive lipid-lowering) 2-year MACCE incidence was 9.52%, and the 1:1 ratio of enrollment according to the overall test level of two-sided α=0.05, test efficacy β=0.80, would result in a single-group sample size of 1,749 cases, a total sample size of 3,498 cases, and a total of 3,684 patients would be needed to account for a 5% dropout rate.to account for a 5% dropout rate.

5.Data management

To ensure the accuracy and authenticity of data collection, the research team unified data quality control training. The data come from the baseline and follow-up data collected by the investigators, and the collected baseline and follow-up data are organized to establish the database. The database will be stored separately by the investigator of this study to ensure that the database is not leaked to the public. During the follow-up survey, the designated study doctor will be responsible for the collection and entry of follow-up data. The data will be entered in pairs, and the results of the entry will be used to identify issues such as missing values, outliers, and logical errors, effectively avoiding mistakes during data entry and merging the databases through the software data comparison function. In order to strengthen the management and quality control of clinical endpoint events, a Clinical Endpoint Event Committee (CEC) will be established to determine the expected endpoint events of the trial under the unified evaluation criteria during and at the end of the trial, so as to more accurately evaluate the results of the trial.

6.The principle of confidentiality

All the data of this study, are stored in Fu Wai Hospital. The researcher strictly abides by the principle of confidentiality in accordance with the regulations. Data desensitization technology is applied to de-identify personal information, protect private data, ensure information security, and collect, extract, and analyze information in the background. All data will be appropriately kept as the basis of the study and will not be used as evidence for other purposes, and only the researcher, the research authority, and the Ethics Committee will be allowed to access the relevant data of the study. The identity of the enrollees and the privacy of their personal data will not be mentioned in any study report. The data and results of this study may be published or made public in paper or electronic form in domestic or foreign medical journals or other media, but the researcher will maintain the confidentiality of the identity of the study participants in accordance with the legal requirements to ensure that the personal information of the study participants will not be disclosed.

7.Quality control of research

Quality control of the main aspects of the study, assessment of whether the collaborating unit has the facilities and conditions required for the study before the investigation is initiated, quality control during the clinical research process, laboratory processes, quality control of data management, division of labor, clarification of duties and authorization of the participating researchers, unified training and monitoring plan for the study protocol and the corresponding operations, and so on.

8. Ethical principle

8.1 Ethical approval

This study protocol will comply with relevant laws and regulations and be approved by the Ethics Committee. In the execution of all aspects of the study, all specifications set forth in the protocol will be strictly followed; the investigator will not modify or change the operating procedures described in this protocol. If any modification of the study protocol and informed consent is required during the study, it will be re-submitted to the Ethics Committee for approval.

8.2 The process of informed consent

Before each subject is enrolled in the study, the investigator will provide him/her or his/her legal representative with the content and instructions of a complete, comprehensive, easy-to-understand, and Ethics Committee-approved informed consent form in written text and give the subject or his/her legal representative sufficient time to consider whether or not to participate in the study. Entry into the study is allowed only after the informed consent is signed by the subject or his/her legal representative. During the study, if new safety information results in a

significant change in the risk/benefit assessment, the subject or his/her legal representative will be provided with all the updated new information, and a new informed consent form will be re-signed.

8.3 Risk minimization

This study firmly adheres to the principle of minimization of risk to subjects regarding informed consent, benefits to subjects (personal and societal benefits) versus risk, confidentiality, and conflict of interest.

9. Organizational management of the study

The project source of this study is the Chinese Academy of Medical Sciences, and it is an investigator-initiated study. The Cardiovascular Metabolism Center of Fu Wai Hospital, as the group leader, and Naqiong Wu, as the specific implementer of this study, are responsible for the overall operation of the study, including the management of the participating collaborators and the monitoring analysis and reporting of the collaborators. Naqiong Wu are responsible for the treatment grouping of eligible subjects, acceptance and processing of data collected by the leader unit (Fu Wai Hospital) and the collaborating units, quality control, and statistical analysis and reporting.

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