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Rationale and design of a randomized controlled trial: The effect of intensive lipid-lowering therapy with PCSK9 inhibitor on endothelial-coverage of stent strut after percutaneous coronary intervention (PCI) for patients with acute coronary syndrome (ACS): Optical coherence tomography (OCT) study (PIECES-OCT study)

Zheng Yin, Zhi-Fan Li, Wen-Jia Zhang, Shuang Zhang, Yong-Gang Sui, Yan-Lu Xu, Hai-Tao Zhang, Xiao-Ning Liu, Hong Qiu, Jing-Lin Zhao, Jian-Jun Li, Ke-Fei Dou, Jie Qian, Yong-Jian Wu **, Na-Qiong Wu *, on behalf of PIECES-OCT investigators

Cardiometabolic Center, National Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Science & Peking Union Medical College, 100037, Beijing, China

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ABSTRACT

Background: For the patients with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT) for at least 1 year is recommended in the guidelines to minimize the risk of stent thrombosis. Persistently uncovered stent strut means delayed neointima formation and extend the window of time in which the stent is prone to thrombosis. Previous studies showed that statins could improve post-stenting strut endothelial coverage for patients undergoing PCI. However, there are lack of evidences on whether early initiation of proprotein convertase subtilisin/Kexin type 9 monoclonal antibody (PCSK9mAb) after PCI in ACS patients can further improve the rate of stent strut coverage on the background of oral lipid-lowering therapy (LLT).

Methods: This is a single-center, randomized trial to enroll 36 patients undergoing PCI with a clinical diagnosis of non-ST-segment elevation ACS. The baseline level of low-density lipoprotein cholesterol (LDL-C) of these patients are between 1.4 mmol/L and 3.4 mmol/L. Patients will be assigned to intensive lipid-lowering therapy (LLT) with PCSK9mAb group and conventional LLT without PCSK9mAb group for 12 weeks in a clinical follow-up setting according to 1: 1 randomization. the rate of stent strut endothelial coverage by optical coherence tomography (OCT) examination at 12 weeks after enrollment between the groups will be compared.

Conclusion: This will be the first study to investigate changes in the rate of stent strut endothelial coverage under intensive LLT with PCSK9mAb by OCT examination in ACS patients undergoing PCI. The finding of this study will provide clinical evidence for future research about the

* Corresponding author. Cardiometabolic Medicine Center, National Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Science and Peking Union Medical College, No 167 BeiLiShi Road, XiCheng District, Beijing, 100037, China.

** Corresponding author. Center of Coronary Heart Disease, National Center for Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Science and Peking Union Medical College, No 167 BeiLiShi Road, XiCheng District, Beijing, 100037, China.

E-mail addresses: yongjianwu_nccd@163.com (Y.-J. Wu), fuwainaqiongwu@163.com (N.-Q. Wu).

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hypothesis of a novel strategy of "intensive LLT (PCSK9mAb + statin ± ezetimibe) combined with shortened DAPT duration" for ACS patients undergoing PCI.
Clinical Trial Registration: URL: https://www.clinicaltrials.gov. Unique identifier: ChiCTR2200063395.

1. Introduction

Acute coronary syndrome (ACS) is a major disease threatening human health. The treatment strategies mainly include medical treatments (both antithrombotic and lipid-lowering therapy, LLT) and coronary revascularization.

Among them, percutaneous coronary intervention (PCI) is an important strategy of treating ACS. For ACS patients undergoing PCI, dual antiplatelet therapy (DAPT) for at least 1 year is recommended in the guidelines to minimize the risk of stent thrombosis. Persistently uncovered stent struts are a symbol of delayed neointima formation and extend the window of time in which the stent is prone to thrombosis [1]. With the development of intravascular imaging, studies have demonstrated that the ratio of uncovered to total stent struts per section, is the most important histologic predictor of late stent thrombosis (LST) [2]. Furthermore, the risk of LST increases as the number of uncovered struts increases and becomes extraordinarily high when the ratio of uncovered to total struts per section is more than 30 % [2].

As the cornerstone of lipid-lowering drugs, numerous evidences showed statins could improve the prognosis of patients with coronary heart disease, including those with acute coronary syndrome (ACS), or undergoing percutaneous coronary intervention (PCI) [3,4]. At the same time, there were evidences that statins could improve post-stenting strut endothelial coverage. In animal models, previous study has demonstrated that atorvastatin pretreatment can accelerate both endothelial coverage and re-endothelialization after sirolimus-eluting stent (SES) implantation, which may be mediated by the mobilization of endothelial progenitor cells (EPC) and enhancement of the endothelial function of the neointima [1]. In vivo study which aimed to explore the effect of 3- and 12-months high-dose statin (atorvastatin 80 mg per day) on drug-eluting stents (DES) stent endothelial coverage, it was confirmed that high-dose statin had a beneficial effect on vascular healing after stent implantation, with the rate of stent endothelial non-coverage of 7.4 % vs 10.6 % (high dose statin group vs. routine dose statin group) in 3 months and 1.3 % vs 2.5 % ($P = 0.01$) in 12 months [5]. In addition, Suh et al. also found that lower low-density lipoprotein cholesterol (LDL-C) levels at follow-up(6-months), especially those with

Table 1
Study inclusion criteria.

Inclusion criteria
Clinical criteria
• Patients aged 18–75 years of both sexes
• Patients with clinically diagnosed NSTE-ACS undergoing PCI
• Patients with a baseline LDL-C between 1.4 mmol/L and 3.4 mmol/L
Angiography inclusion criteria
• Patients with less than 2 primary lesions in situ planned for interventional surgery (Including 1 lesion in one vessel, 1 lesion in each vessel, or 2 lesions in one vessel)
• The diameter of the lesion is visual≥50 % and <100 %
• The RVD must be between 2.5 and 4.0 mm
PCI inclusion criteria
• Stent type specified by the institute
Exclusion criteria
• Severe heart failure (Killip class III or IV) or cardiogenic shock, LVEF <30 %
• Previous history of cerebrovascular disease
• Hepatic or renal insufficiency (e.g., eGFR<60 ml/m2 or serum creatinine level >2.5 mg/dL, or dialysis ongoing) or creatine kinase elevation >5 times the upper limit of normal
• Previous history of a malignant tumor
• Patients who are intolerant to statins or ezetimibe
• Patients who are intolerant to injection
• Patients with other medical conditions (e.g., cancer, neuro-deficient stroke) or a history of substance abuse (alcohol, etc.); May not comply with the protocol, affect the interpretation of relevant data or have a limited lifespan (i.e., less than 1 year) in the judgment of the doctor.
• Patients with poor adherence
• Patients with indications for anticoagulation
• Patients with allergies or contraindications to aspirin, heparin, bivalirudin, antiplatelet agents (clopidogrel, and ticlopidine), rapamycin, lactate polymers, contrast media, or stainless steel
• Female patients who are pregnant or breastfeeding, or women of gestational age who are not using contraception
OCT exclusion criteria
• The target vessels were severely distorted, calcified, and angulated, after the assessment of researchers, the placement of an OCT catheter is believed to cause risks or complications
• Chronic complete occlusion of the target vessel or its TIMI blood flow level is zero
Exit criteria
• Patients may withdraw from the study at any time, for any reason, and without suffering any sanction for doing so

NSTE-ACS Non-ST-Segment Elevation Acute Coronary Syndrome; PCI, Percutaneous Coronary Intervention; RVD, Reference Lumen Diameter; LVEF, Left Ventricle Ejection Fraction; eGFR, evaluation Glomerular Filtration Rate; OCT, Optical Coherence Tomography.

LDL-C<1.8 mmol/L, might have a protective effect against delayed strut coverage after DES implantation. In this study, it was found that the rate of non-coverage strut in the <1.8 mmol/L group was significantly lower compared with that in >1.8 mmol/L group (10.1 % vs 26.9 %, P = 0.025) [6].

Previous studies have confirmed that PCSK9mAb can reduce LDL-C to a very low level and improve the prognosis of ACS. Large-scale outcome RCTs have shown that PCSK9mAb reducedd LDL-C to the range of 0.78–1.04 mmol/L (30–40 mg/dL) and improved the incidence of major adverse cardiovascular events (MACEs), with hazard ratio (HR) of 0.85 [7,8].

Moreover, recently it was reported concerning long-term PCSK9mAb treatment could improve plaque stabilization and promote plaque regression. In HUYGENS study, it was demonstrated that in evolocumab group, there was a greater increase in minimum fibrous cap thickness (+42.7 vs + 21.5 μm, P = 0.015) and decrease in maximum lipid arc (−57.5° vs. −31.4°, P = 0.04) throughout the arterial segment [9]. In GLAGOV study, percent atheroma volume (PAV) increased 0.05 % with placebo and decreased 0.95 % with evolocumab (−1.0 %, P < 0.001), while total atheroma volume (TAV) decreased 0.9 mm^3 with placebo and 5.8 mm^3 with evolocumab (−4.9 mm^3, P < 0.001) [10]. Furthermore, EVOPACS study pointed out that the use of PCSK9 mAb initiated during hospitalization of ACS could achieve rapid (in 8 weeks) and significant reduction (by 2.82 mmol/L) of LDL-C levels [11]. However, there are few studies on whether early initiation of PCSK9mAb after PCI in ACS patients can improve the rate of stent strut endothelial coverage of them. In our study, we aim to investigate early initiation of PCSK9mAb after PCI in ACS patients can further improve the rate of stent strut endothelial coverage on the background of statin ± ezetimibe LLT.

2. Method

2.1. Study design

This study is a single-center, randomized controlled study conducted in Fuwai Hospital. It aims to investigate the intensive LLT with early initiation of PCSK9mAb in the acute episode of ACS. Compared with the conventional LLT without PCSK9mAb, it is expected to further improve the rate of stent strut endothelial coverage in ACS patients undergoing PCI.

2.2. Patient enrollment and randomization

This study will enroll 36 NSTE-ACS patients aged 18–75 years of both sexes, undergoing PCI and whose baseline LDL-C between 1.4 and 3.4 mmol/L. All patients were treated with the background of oral LLT only. Inclusion criteria for angiography and PCI such as specific coronary lesion are also required for enrollment in this study. Patients with systemic diseases may be excluded, which are described in Table 1 in detail.

2.3. Treatment and follow-up procedures

Eligible patients will be screened and randomly assigned (1:1) to intensive LLT (PCSK9mAb + statin + ezetimibe) group (G1, n = 18) or conventional LLT (statin + ezetimibe) group (G2, n = 18) by interactive response technology (IRT) system. After randomization, the oral LLT strategy in both groups will be the same. The definition of oral LLT is moderate-dose statin ± ezetimibe. Moderate-dose statins included atorvastatin 20 mg daily, rosuvastatin 5–10 mg daily, fluvastatin (sustain-released dose) 80 mg daily, pitavastatin 2–4 mg daily, simvastatin 20 mg daily, pravastatin 40 mg daily, the daily dose of ezetimibe is 10 mg for each patient. In G1, the patients received PCSK9mAb injection every 2 weeks with evolocumab (140 mg ih).

Table 2
Schedule of enrollment, assessments, interventions, and follow-up.

	Screening	Visit 1	Visit 2
TIME POINTS	0 days	4 Weeks ±7 days	12 Weeks ±7 days
ENROLLMENT			
Eligibility criteria	X		
Exclusion criteria	X		
Informed consent	X		
ASSESSMENTS			
Physical examination	X		
Medical and cardiovascular disease history	X		
CBC	X		X
Biochemical examination	X		X
Angiography	X		X
OCT examination	X		X
(Severe) adverse event monitoring		X	X
DRUG TREATMENT			
Experiment Group (PCSK9mAb + statin + ezetimibe)	X	X	X
Control Group (statin + ezetimibe)	X	X	X

The X symbol indicates the specific time point at which the corresponding measurement will be taken. Random means any time after angiography but before Visit 1. CBC means Complete Blood Counts.

Optical coherence tomography (OCT) will be performed in each group. It is defined as the need for target single-vessel coronary artery confirmed by coronary angiography. During PCI, OCT will be used to confirm that the stent is well dilated and adhered to the vessel wall.

Study follow-up will occur at 4 and 12 weeks after enrollment. On the day of enrollment (Day 0), patients will be asked to sign the informed consent, while a variety of general, physical and laboratory examination will be performed. Coronary angiography and OCT examination will also be conducted. A telephone call will be performed at the end of 4 weeks to follow up the patient's tolerance to the corresponding treatment. At the end of the trial (week 12), the patient will be re-hospitalized, and laboratory examination, coronary angiography and OCT examination will be performed. During the follow-up, the patients will also be followed up for adverse event monitoring. Treatment of the corresponding group will start in the eligible patients at the day of enrollment, with PCSK9mAb + statin ± ezetimibe in G1 and statin ± ezetimibe in G2, which will continue until Week 12. Patients could withdraw from the study any time for any reasons without any consequences. All the details of the follow-up procedure are shown in Table 2.

The primary endpoint is designed as the rate of stent strut endothelial coverage assessed by OCT examination and calculation in both the groups at week 12 during the follow-up. The flow chart describing the whole procedure of enrollment and follow-up is shown in Fig. 1.

2.4. Quantitative coronary angiography (QCA)

QCA analysis is conducted both pre- and post-stent implantation, along with a 12-week follow-up assessment. These analyses are carried out using an offline quantitative coronary angiographic system (specifically, the Philips Azurion 7M20), overseen by an independent core laboratory located at the Cardiovascular Research Center in Beijing, China. Reference vessel diameter and minimum luminal diameter are measured based on diastolic frames, all within a single, matched view that captures the smallest minimum luminal diameter.

2.5. OCT imaging and analysis

Mandatory baseline inclusion involves an OCT examination. Subsequently, patients will undergo examinations immediately post-procedure and at the 12-week mark following discharge. Target lesion imaging is conducted using the frequency-domain OCT system, Optimiro HS100 Intravascular OCT System, produced by Horimed Technology Co., Ltd in Tianjin, China. The OCT cross-sectional images are created at a rotational speed of 100 frames per second, with the fiber being retracted at a rate of 20 mm per second within the stationary imaging sheath. All OCT images are subject to analysis at the core laboratory situated at the Cardiovascular Research Center in Beijing, China. Importantly, the analysts conducting the analysis remain blinded to patient and procedural information. Meticulous analysis of cross-sectional OCT images was performed at 0.2-mm intervals. The quantification of the cross-sectional areas (CSAs) of both the stent and the lumen was carried out, and the CSAs of neointimal hyperplasia (NIH) was derived by subtracting the luminal CSA from the stent CSA. The thickness of NIH was calculated by measuring the distance between the inner

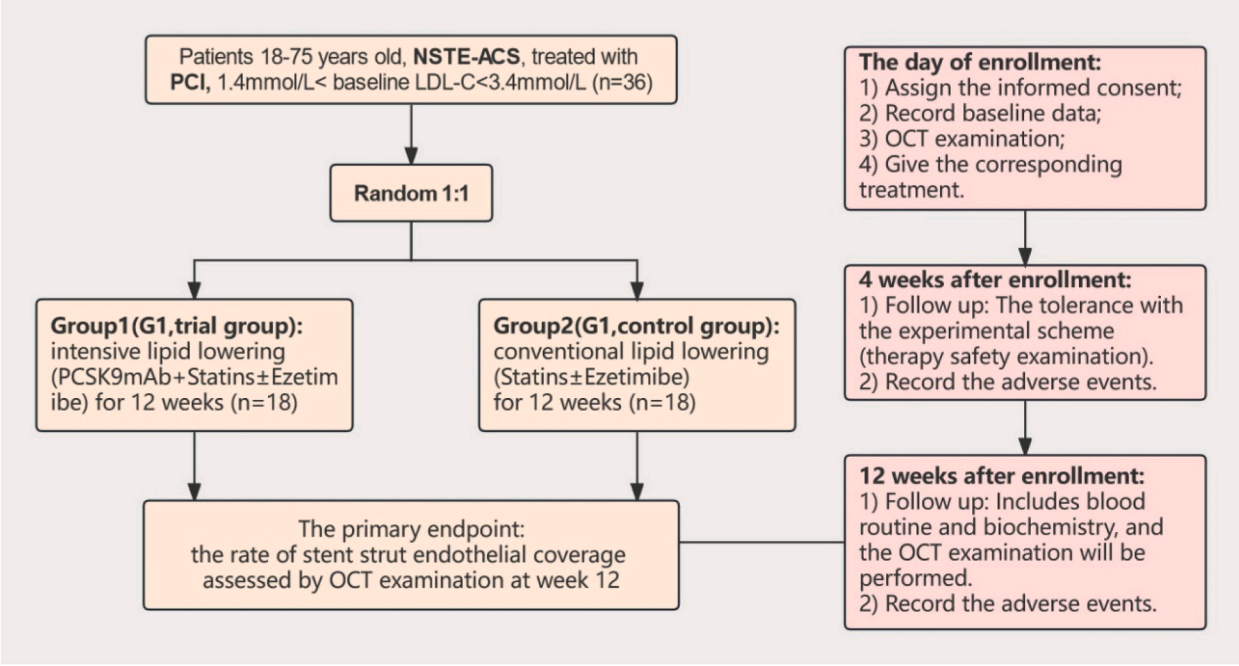

Fig. 1. Flowchart of the randomized clinical trial.

surface of the neointima and the stent strut. An uncovered strut was recognized when the thickness of NIH measured 0 μm [12,13]. A malapposed strut is defined as a strut that had detached from the vessel wall by ≥ 160 μm in SES [12,14]. Calculating the respective ratio of uncovered or malapposed struts to the total struts in all OCT cross sections can get the percentage of uncovered or malapposed struts. Stent malapposition is defined as the presence of malapposed struts [15]. To assess the extent of malapposition, measurements include the total extra-stent luminal volume, the maximum extra-stent luminal CSA, and the maximum distance between the malapposed strut and the vessel wall Intrastent thrombi are characterized as an irregular mass protrusion into the lumen with a thickness of at least 250 μm at its widest point [16]. The total stent length was measured at baseline and during the 12-week follow-ups, with confirmation of unchanged stent length across all lesions for serial comparisons [17,18]. The cross-sectional OCT images obtained during the 12-week follow-ups are rigorously aligned based on the distance from the stent edge and key landmarks, including side branches, ostium location, and calcified plaques. All OCT images are measured at an independent imaging core laboratory and the quality control is done regularly. OCT examination have been determined to differ between observers in the prior study, including the measured distances and areas [18]. Therefore, forty cross-sectional OCT images were randomly selected at 12-week and measured twice by a same analyst in different time point, and once by two different analysts.

2.6. Statistical considerations

Statistical analysis is conducted using R version 3.12 (R Development Core Team, Vienna, Austria, http://www.R-project.org). Categorical data are expressed in terms of numbers and percentages, and comparisons are made using chi-squared statistics or Fisher's exact test as appropriate. Continuous data are presented as mean ± standard deviation and compared using Student's t-test or paired *t*-test. In cases where data distributions are skewed, medians with interquartile range are provided, and non-parametric tests are employed for comparisons. A two-sided p-value less than 0.05 is considered statistically significant. Cross-sectional and strut-level data are analyzed using a hierarchical multilevel regression model to address the clustering issue at the individual patient/lesion level. Repeated-measure analysis of variance is also conducted to compare the groups across different time intervals. Inter- and intra-observer agreements in the measurements of the rate of stent strut endothelial coverage are assessed using the intra-class correlation coefficient (ICC) and Cohen's κ, respectively. This assessment involves 40 randomly selected cross-sectional images analyzed by two independent readers and the same reader at two separate time points.

2.7. Sample size and power

The sample size in this study is based on the expective different outcomes between those two groups. According to previous related results in some trials, less than 5 % non-coverage can prevent the development of LST, the rate of stent strut endothelial non-coverage in G1 and G2 is pre-designed as 4 % and 6 %, respectively, with a two-tailed significance level of 0.05. 5094 stent wire structures need to be detected, assuming that each patient is implanted with one stent, and each stent has 180 stent wires on average, according to the 1:1 parallel high-efficiency design, alpha = 0.025, power = 85 %, a total of 28 cases need to be selected subject. Assuming the 20 % attrition rate, 36 subjects will be planned to be recruited, randomize 1:1 into G1 and G2.

3. Data management

3.1. Discussion

To the best of our knowledge, this will be the first study to investigate whether PCSK9mAb therapy could further improve the rate of coronary stent strut of endothelial coverage by OCT evaluation in ACS patients undergoing stent implantation.

In general, a series of pathophysiological changes occur after PCI. Starting from the injury of the vessel wall, inflammatory mediators are released, promoting local platelet aggregation, leading to the formation of local blood turbulence, affecting the hemodynamics at the stent strut endothelial coverage [19]. At the same time, EPCs can migrate and proliferate in the peripheral blood in response to vascular injury, contributing to the neovascularization process by differentiating into endothelial cells [20].

The stent strut endothelial coverage after stent implantation to avoid contact between foreign bodies and vascular flow is an indicator of post-PCI repair and could predict prognosis of ACS patients undergoing PCI [21]. However, following stenting, the regenerated endothelium may be abnormal in terms of both integrity and function, with areas of poor endothelization, poorly formed endothelial cells junctions, reduced expression of anti-thrombotic molecules and decreased NO production, therefore still portending a relevant risk of future serious complications [22,23].

OCT enabled in vivo assessment of stent strut endothelial coverage and allow us to calculate vascular repair index [24]and to identify predictors associated with a delayed vessel wall healing. In particular, stent design (i.e., stent polymer, stent strut thickness, and drug elution), strut embedment and apposition, the composition of the underlying plaque, and the time interval between stent implantation and follow-up imaging seem to determine strut endothelial coverage [25]. Previous studies on the relationship between stent endothelial coverage and LST have shown that less than 5 % non-coverage can prevent the development of LST.

EPC is an important factor affecting the stent strut endothelial coverage. Previous studies demonstrated that circulating bone marrow derived EPCs move to sites of neovascularization and differentiate into endothelial cells in situ in a manner consistent with a process termed vascular genesis [26,27]. The changes of EPC function and number after PCI are still controversial. Thomas HE et al. demonstrated that the local endothelial injury following PCI induce a reduction in circulating EPCs by 15 % in 6 h [28]. However, this is in contrast to the increase in post-PCI EPCs levels observed by Lee et al. [29]. A possible explanation of these discordant findings can

be found in the study of Gao et al. who demonstrated that elective PCI triggers a time-dependent mobilization of CD34+/KDR + cells that closely correlates with the extent of the endothelial injury caused by the procedure [30].

Statins are the most widely used lipid-lowering agents in patients with coronary artery disease (CAD). A novel mechanism of statin treatment in patients with stable CAD was found as the augmentation of circulating EPCs with enhanced functional activity [31]. Hibbert B et al. reported that high dose atorvastatin therapy pre-PCI improved EPC number and function in humans which may in part explain the benefit in clinical outcomes seen in patients undergoing coronary interventions [32]. In addition, they could reduce inflammation and enhance endothelial function via pleiotropic effects [33]. Previous in vitro and animal studies reported that statins could regulate the migration and proliferation of smooth muscle cells and control neointimal formation [34].

However, there are few studies on PCSK9 and EPC functions. A recent cross-sectional clinical study in humans indicated the effects of PCSK9 on EPCs functions. Namely, endogenous PCSK9 levels were inversely correlated with circulating EPC count in patients with type 2 diabetes mellitus on statin therapy, as well as in the entire cohort of patients [35], which suggested that the increase of endogenous PCSK9 level is related to the EPC dysfunction. While another study showed significantly higher EPC counts and proliferative capacity in patients treated with PCSK9mAb, detected as early as one month after treatment initiation. Increased VEGF levels are accompanied by the effect of PCSK9mAb [36].

Platelets, lipids, inflammation and plaque stability also have an impact on stent strut endothelial coverage. Plasma PCSK9 levels are elevated in ACS patients, which associated with atherosclerotic plaque instability, inflammatory response, and platelet reactivity [37, 38]. PCSK9mAb can potentially deplete cholesterol on platelet membranes by significantly reducing LDL-C levels. Its inhibitory effect on platelet activation may also be mediated by a reduction in the ability of platelets to oxidize LDL, thereby reducing the latter's ability to stimulate platelet activity through the CD36 and LOX- 1 receptor pathways [39]. Furthermore, PCSK9mAb may also reduce lipoprotein (a) levels, a major carrier of oxidized phospholipids, potentially impairing their ability to activate platelets through toll-like receptor 2 (TRL2) receptors [40]. PCSK9mAb also increase high-density lipoprotein (HDL), decrease platelet activation at apoER2 and SRB1 receptors, and clear cholesterol from platelet membranes [41]. PCSK9mAb enhance hepatic LDL-R expression through both intracellular and extracellular mechanisms and may also enhance LRP-1 expression [42], potentially enhancing FVIII internalization and degradation, resulting in a decrease in FVIII plasma levels [43]. In addition, PCSK9mAb may also reduce the activity of circulating tissue factor (TF) by activating of TLR4/NFkB signaling and accelerating TFs clearance [44].

Multiple studies have shown that the application of PCSK9mAb in ACS patients can significantly reduce MACE in ACS patients through, intervention in lipid metabolism platelet aggregation, plaque modification and improve endothelial dysfunction [45,46].

The finding of this study will provide clinical evidence for future research on the hypothesis of a novel strategy of "intensive LLT (PCSK9mAb + statin + ezetimibe) combined with shortened DAPT duration" for ACS patients undergoing PCI. And if the rate of stent strut endothelial coverage is high enough through early initiation of PCSK9mAb for ACS patients undergoing PCI, DAPT duration could be shortened with no increasing risk of stent thrombosis. Moreover, early discontinuation of DAPT therapy can reduce the occurrence of adverse bleeding events, especially will be beneficial for those patients with high bleeding risk. It will provide reliable evidence about early initiation of PCSK9mAb therapy for ACS patients undergoing PCI.

4. Limitations

Firstly, although our study is designed as a randomized trial, the study population included a relatively small number of patients. Secondly, this trial is not designed as a blinded trial due to unattainable placebo for PCSK9mAb. Thirdly, this trial is designed to enroll the patients with simple coronary artery lesions, not the patients with complex lesions, or with complete occlusion of target vessels. Finally, the rate of stent strut endothelial coverage cannot be clearly evaluated in lesions with a thin neointima >10–15 μm in thickness because the axial resolution of OCT is 10–15 μm [47].

Registration detail

This clinical trial is registered on https://www.clinicaltrials.gov with the number ChiCTR2200063395.

Ethics statement

The ethics approval number is 2022-1746, and the ethics committee is Ethics Committee of Fuwai Hospital, CAMS&PUMC.

Sex and gender statement

Sex and gender are not relevant to this research.

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Data availability statement

No new data were generated or analyzed in support of this research. No data associated with this study was deposited into a

publicly available repository as this is a study protocol and no data was generated in this manuscript. The data of this trial will be managed by the corresponding authors after the trial is completed, and will be made available upon reasonable request.

CRediT authorship contribution statement

Zheng Yin: Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Zhi-Fan Li:** Methodology, Writing – original draft. **Wen-Jia Zhang:** Methodology, Conceptualization. **Shuang Zhang:** Methodology, Conceptualization. **Yong-Gang Sui:** Methodology. **Yan-Lu Xu:** Methodology. **Hai-Tao Zhang:** Methodology. **Xiao-Ning Liu:** Methodology. **Hong Qiu:** Methodology. **Jing-Lin Zhao:** Methodology. **Jian-Jun Li:** Methodology. **Ke-Fei Dou:** Methodology. **Jie Qian:** Methodology. **Yong-Jian Wu:** Methodology. **Na-Qiong Wu:** Conceptualization, Methodology, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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