BMJ Open

Alirocumab effect on preventing periprocedural ischaemic events in coronary heart disease patients undergoing coronary stenting (APPEASE trial): study protocol of a multicentre, open-label, randomised controlled trial

Zhuoshan Huang,[1,2,3] Xiaodong Zhuang ,[2,3] Shaozhao Zhang ,[2,3] Yiquan Huang,[2,3] Lianxiong Yuan,[4] Aiwen Lin,[5] Leile Tang,[1] Zhenyu Xiong,[2,3] Odong Christopher,[2,3] Yang Chen,[1] Bingyuan Wu,[1] Yesheng Ling,[1] Suhua Li,[1] Qiang Jie,[5] Longgen Xiong,[6] Xiaoxian Qian,[1] Xinxue Liao ,[2,3] Jinlai Liu [1]

To cite: Huang Z, Zhuang X, Zhang S, *et al*. Alirocumab effect on preventing periprocedural ischaemic events in coronary heart disease patients undergoing coronary stenting (APPEASE trial): study protocol of a multicentre, open-label, randomised controlled trial. *BMJ Open* 2023;**13**:e072541. doi:10.1136/bmjopen-2023-072541

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-072541).

ZH and XZ contributed equally.

Received 11 February 2023
Accepted 26 June 2023

For numbered affiliations see end of article.

Correspondence to
Professor Jinlai Liu; liujinl@mail.sysu.edu.cn and Dr Xinxue Liao; liaoxinx@mail.sysu.edu.cn

ABSTRACT

Introduction Percutaneous coronary intervention (PCI)-related myocardial infarction (type 4a MI) and major periprocedural myocardial injury have been demonstrated leading to poor prognosis of patients with coronary heart disease (CHD) undergoing elective PCI and still remain high occurrence even after the therapy of dual antiplatelet agents and statins. Proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab has been shown to be effectively in reducing the risk of acute MI (AMI). However, the effect of alirocumab on preventing PCI-related MI or major periprocedural myocardial injury in patients with CHD undergoing elective PCI remains uncertain.

Methods and analysis Alirocumab effect on Preventing Periprocedural ischaemic Events in coronary heart diseAse patients undergoing coronary StEnting trial is a multicentre, open-label, randomised controlled trial aiming to determine whether alirocumab could reduce the incidence of type 4a MI or major periprocedural myocardial injury in patients with CHD undergoing elective PCI. In total, 422 non-AMI CHD patients planned to undergo elective PCI will be randomly assigned to receive standard pharmacotherapy of CHD (control group) or additional use of subcutaneous alirocumab 75 mg 1 day before procedure (alirocumab group). The primary outcome is type 4a MI or major periprocedural myocardial injury defined as high-sensitivity cardiac troponin elevating above 5×99th percentile upper reference limit in 48 hours after PCI. Patients will continue receiving standard pharmacotherapy or additional biweekly subcutaneous alirocumab 75 mg for 3 months according to the initial randomisation group. We will follow up for 3 months and record all the major adverse cardiovascular events (MACEs). Incidence of PCI-related MI or major periprocedural myocardial injury, and MACE in 3 months after PCI will be compared between control group and alirocumab group.

Ethics and dissemination Ethics approval has been obtained from the Medical Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University with approval number: (2022)02-140-01. The results of this study will be reported through peer-reviewed journals and conference presentations.

Trial registration number ChiCTR2200063191.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will provide new evidence of the efficacy of alirocumab on preventing percutaneous coronary intervention (PCI)-related myocardial infarction or major periprocedural myocardial injury in patients with coronary heart disease undergoing elective PCI.
⇒ The results of this study will provide reliable evidence for the periprocedural use of proprotein convertase subtilisin/kexin type 9 inhibitors in elective PCI.
⇒ This is a multicentre, open-label, randomised controlled trial for data of high quality of evidence.
⇒ Although we will blind all the operators who perform the operation, the open-label of patients and investigators may have the inherent drawbacks of investigator bias.

INTRODUCTION

Percutaneous coronary intervention (PCI) on the basis of pharmacological therapies is the major treatment strategy for coronary heart disease (CHD) with severe coronary stenosis. As the technical advances in PCI and development in new pharmacological therapies, the rates of severe PCI-related complications

such as acute stent thrombosis, stroke and vascular access bleeding has been drastically decreased.[1–3] Therefore, elective PCI in patients with stable CHD is considered to be a safe procedure. However, elevation in cardiac biomarkers which is defined as type 4a myocardial infarction (MI) and periprocedural myocardial injury is still frequent, especially in the era of high-sensitivity cardiac troponin (hs-cTn).[4] Previously, prognostic significance of different postoperative cTn elevation in patients with CHD undergoing elective PCI remained controversial, especially for those asymptomatic patients with minor myocardial injury. Nevertheless, Silvain *et al* pooled all the relevant data of previous studies in patient-level and eventually certificated that post-PCI cTn elevation of >5×99 th percentile upper reference limit (URL) was strongly associated with 1 year mortality.[5] Therefore, the consensus document by the European Society of Cardiology (ESC) Working Group on Cellular Biology of the Heart and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) defined the prognostically relevant major periprocedural myocardial injury as post-PCI cTn elevation>5×99 th percentile URL.[6] As the poor prognosis, appropriate treatment strategies for reducing the risk of PCI-related MI or major myocardial injury are necessarily to be explored.

Current management for preventing periprocedural MI and injury in patients with CHD undergoing elective PCI included dual anti-platelet therapy, high-dose statins and anti-inflammatory agent such as colchicine.[6] Previous studies have already demonstrated the effectiveness in reducing periprocedural MI of anti-platelet[7] and statins therapies[8] given prior to PCI. However, even with adequate dose of dual-platelet drugs (aspirin combining clopidogrel or aspirin combining ticagrelor) and statins, occurrence of PCI-related MI or major myocardial injury still remained relatively high.[9] It is mainly due to the complexity of the pathogenesis in myocardial injury during PCI. The aetiologies of periprocedural myocardial injury and type 4a MI include side branch occlusion, distal thromboembolism or lipid embolism, coronary dissection or perforation, microvascular no-reflow, endothelial dysfunction, impaired coronary vasomotion, inflammation and etc, alone or combination[6 10–14] (figure 1A). Furthermore, our previous studies demonstrated the association between lipid profile including low-density lipoprotein cholesterol (LDL-C) and lipoprotein(a) and the risk of periprocedural myocardial injury.[15 16] Therefore, the treatment strategies for preventing periprocedural MI and injury may focus on these underlying risk factors and aetiologies.

Proprotein convertase subtilisin/kexin type 9 (PCSK9), which is secreted by the liver and combines the LDL receptor (LDLR) to form the PCSK9-LDLR complex internalised by endosomes, has been reported to play an important role in the development of atherosclerosis.[17 18] The PCSK9 inhibitors evolocumab and alirocumab which could significantly reduce LDL-C and Lp(a) levels have been already proven to be an effective strategy to reduce

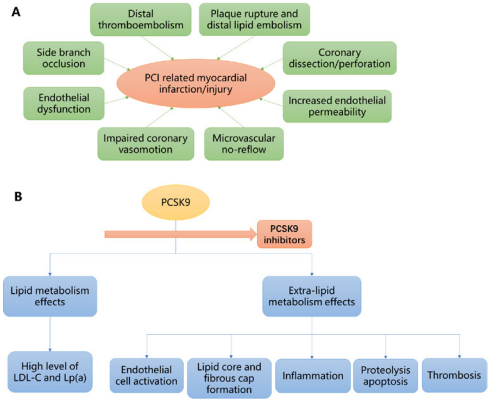

Figure 1 Physiopathological mechanisms of PCI-related myocardial infarction/injury and PCSK9. (A) Aetiology of type 4a myocardial infarction and PCI-related myocardial injury. (B) Atherogenic mechanisms of PCSK9 and effect of PCSK9 inhibitors. LCI-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9.

the risk of MI among patients with or without known cardiovascular diseases.[19–22] In addition, recent studies have demonstrated the non-classical mechanisms of PCSK9 in atherosclerosis including endothelial cell activation, inflammation, proteolysis apoptosis, lipid core formation, platelet activation and thrombosis[23–25] (figure 1B). Therefore, mechanically, we deduce that PCSK9 is associated with periprocedural myocardial injury during PCI. As alirocumab could significantly and promptly decrease serum PCSK9 levels[26] and further inhibit the classical and non-classical atherogenic mechanisms of PCSK9,[27–29] we consider that the use of alirocumab before elective PCI could effectively reduce the occurrence of PCI-related MI or major myocardial injury. To test this hypothesis, we designed the Alirocumab effect on Preventing Periprocedural ischaemic Events in coronary heart diseAse patients undergoing coronary StEnting (APPEASE) trial.

METHODS

Overall study design

The APPEASE trial is an investigator-initiated, multicentre, prospective, randomised, parallel controlled, open-label trial to evaluate the efficacy of alirocumab in preventing periprocedural MI and major myocardial injury in patients with CHD undergoing elective PCI. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Approval of the protocol and informed consent forms was obtained from the institutional ethics committee at all study sites, and written informed consent was obtained from all patients. This trial has been registered in Chinese Clinical Trial Registry as identifier ChiCTR2200063191.

Study objectives and endpoints

The primary objective of the APPEASE trial is to investigate whether 75 mg alirocumab by subcutaneous injection

Table 1 Study objectives and endpoints of APPEASE trial

Study objective	Corresponding endpoint
Primary objective	Primary endpoint
► To determine whether preprocedural use of alirocumab could reduce the occurrence of PCI-related MI or major periprocedural myocardial injury in patients with CHD.	► PCI-related myocardial infarction or major myocardial injury, defined as hs-cTn elevating above 5×99th percentile URL within 48 hours after PCI.
Secondary objectives	Secondary endpoints
► To explore the effect of alirocumab on reducing any degree of periprocedural myocardial injury during PCI.	► Different elevation of hs-cTn including hs-cTn above 1×99th percentile URL to 70×99th percentile URL within 48 hours after PCI.
► To explore the effect of alirocumab on improving the short-term prognosis in patients with PCI-related MI or major myocardial injury.	► MACE occurrence at 3 months follow-up after PCI. ► All cause death at 3 months follow-up after PCI.

APPEASE, Alirocumab effect on Preventing Periprocedural ischaemic Events in coronary heart diseAse patients undergoing coronary StEnting; CHD, coronary heart disease; hs-cTn, high-sensitivity cardiac troponin; MACE, major adverse cardiovascular events; MI, myocardial infarction; PCI, percutaneous coronary intervention; URL, upper reference limit.

1 day before elective PCI could reduce the occurrence of periprocedural MI and major myocardial injury in patients with CHD. Correspondingly, the primary study endpoint is PCI-related MI or major myocardial injury which is defined as hs-cTn elevating above 5×99 th percentile URL within 48 hours after PCI regardless of any cause in our study (table 1). The secondary objectives are to demonstrate the effect of alirocumab on reducing any degree of periprocedural myocardial injury during PCI and improving the short-term prognosis in patients with PCI-related MI or major myocardial injury. Therefore, the secondary study endpoints include (1) different elevation of hs-cTn including hs-cTn above 1×99 th percentile URL to 70×99 th percentile URL within 48 hours after PCI; (2) major adverse cardiovascular events (MACE) at 3 months follow-up after PCI and (3) all cause death at 3-month follow-up after PCI (table 1). MACEs are defined as the composite outcomes of cardiovascular death, non-fatal MI, unstable angina requiring hospitalisation, unplanned revascularisation and acute heart failure.

Study population

The study will enrol 422 non-acute MI CHD patients who have never used PCSK9 inhibitors before and undergo elective PCI after admission. Recruitment of patients have already started in September 2022 and planned to end in December 2023. The study is planned to be completed in March 2024. Inclusion criteria and exclusion criteria shown in box 1. We will recruit patients with high suspicion of CHD but not determined yet before procedure. Participants will perform coronary angiography first to identify coronary status, then PCI will be performed for those patients with severe coronary artery stenosis. We will exclude the participants who have not undergo PCI with stent implantation. Therefore, in order to screen out patients with CHD necessary for PCI more appropriately, we develop the inclusion criteria of high-risk features (box 1). Furthermore, we include patients with baseline LDL-C levels above 3.4 mmol/L making the use of alirocumab with indication.

Patient and public involvement

Neither patients or the public were involved in the study design or conduct, and will not be involved with the reporting or dissemination plans of the research.

Study procedures

Patients fulfilling the inclusion criteria and without any exclusion criteria who agree to participate to the protocol and have signed the inform consent will be randomly assigned in a 1:1 ratio to either alirocumab group or control group with the use of a computerised randomisation system involving study-group assignments (www.sealedenvelope.com). Each patient receives sufficient dose of dual antiplatelet (aspirin and clopidogrel, or aspirin and ticagrelor) and statins (atorvastatin or rosuvastatin) therapies before procedure. Then patients in alirocumab group will additionally receive alirocumab 75 mg by subcutaneous injection 1 day before PCI. Baseline hs-cTn, ECG, echocardiography and all other laboratory testing will be evaluated within 3 days before PCI. Furthermore, postoperative hs-cTn and ECG will be evaluated in 6–24 hours after PCI. All patients will continue to receive drug therapy for secondary prevention of CHD after PCI. Patients in alirocumab group will additionally receive alirocumab 75 mg by subcutaneous injection once every 2 weeks for 3 months. We will follow up for 3 months and record all the MACE occurrence (figure 2).

Cardiac biomarkers

Our protocol recommends measuring hs-cTn 6–24 hours after PCI for the primary endpoint assessment. If multiple measurements are performed in 48 hours after PCI, the peak values are considered for analysis. Baseline and postoperative hs-cTn can be measured for hs-cTnI or hs-cTnT as long as the same assay is used for the same patient.

Box 1 Eligibility criteria for APPEASE trial

Inclusion criteria

⇒ Consent to enrollenrol in the study.
⇒ Male or female patients over 18 years old.
⇒ Patients with CHD planned to undergo elective coronary angiography to confirm coronary lesions and further undergo PCI to implant drug-eluting stents releasing coronary stenosis.
⇒ Baseline LDL-C levels exceed 3.4 mmol/L (130 mg/dL).
⇒ Patients meet at least one of the following criteria of (1)(2)+ at least one of the following criteria of (3)–(8).
1. Patients have undergone coronary CT angiography or coronary angiography before, and found the stenosis of more than 70% in at least one of the main coronary artery (LM, LAD, LCX or RCA).
2. Patients with symptoms of angina pectoris that meet the following three characteristics: retrosternal discomfort, featured by its character and duration; induced by fatigue or emotional stress; relief within minutes with rest and/or nitrates.
3. Patients with diabetes.
4. Patients with hypertension.
5. Patients with hypercholesterolaemia, including TC≥6.2 mmol/L or LDL-C≥4.1 mmol/L.
6. Smoking history, including current smoker or former smoker.
7. Obesity, defined as BMI≥28 kg/m^2.
8. Family history of premature cardiovascular disease, defined as CHD occurred in male <55 years old or female <65 years old in first-degree relatives.

Exclusion criteria

⇒ Acute myocardial infarction occurred within the past 3 months.
⇒ Preoperative hs-cTn levels exceeded higher than normal.
⇒ Moderate to severe hepatic insufficiency (ALT or AST>2 times the upper limit of normal).
⇒ Severe renal insufficiency (eGFR<30 mL/min/1.73 m^2).
⇒ Severe anaemia (HGB<60 g/L).
⇒ Pregnant or breastfeeding women.
⇒ Patients who are reluctant to receive alirocumab therapy for 3 months.
⇒ Rotational atherectomy is used during PCI.
⇒ Implant drug eluting balloons or biodegradable stents.
⇒ No stent is implanted.

AST, aspartate transaminase; ALT, alanine transaminase; BMI, body mass index; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; hs-cTn, high-sensitivity cardiac troponin; HGB, haemoglobin; LDL-C, low-density lipoprotein cholesterol; LM, left main coronary artery; LAD, left anterior descending branch; LCX, left circumflex artery; PCI, percutaneous coronary intervention; RCA, right coronary artery; TC, total cholesterol.

Hs-cTnI is analysed by chemiluminescence method through Abbott Architect i2000SR chemiluminescence analyser, while hs-cTnT is analysed by electrochemiluminescence method through Roche Cobas 8000/e602 immunoanalyzer. Their upper limit of normal are defined as the 99th percentile URL of a normal reference population.

Coronary angiography and PCI

Although APPEASE trial is an open-label trial, we will blind all the operators who perform coronary angiography and PCI. Coronary angiography will be performed first to identify coronary artery lesions, then PCI indication will be determined by two experienced interventional cardiologists according to Chinese guideline for PCI.[30] PCI is performed by experienced interventional cardiologists and drug-eluting stents will be implanted to relieve the severe narrowing of coronary artery. Patients receive 100 U/kg bolus intravenous heparin immediately before PCI, and additional bolus dosing to maintain an activated clotting time (ACT) of >250 s.

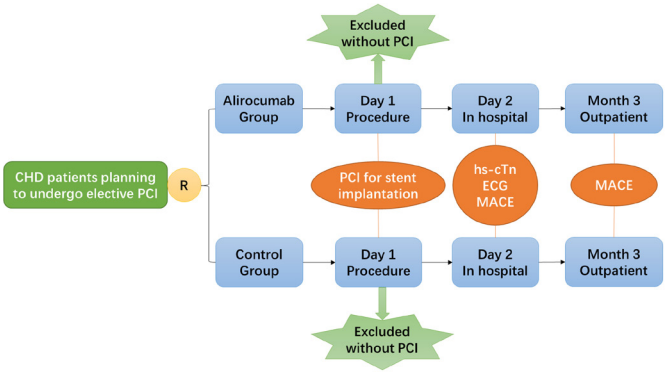

Figure 2 Study design and flow chart of APPEASE. APPEASE, Alirocumab effect on Preventing Periprocedural ischaemic Events in coronary heart diseAse patients undergoing coronary StEnting; CHD, coronary heart disease; hs-cTn, high-sensitivity cardiac troponin; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; R, randomise.

Sample determination and statistical analyses

We aim to evaluate the reduction in the occurrence of PCI-related MI or major myocardial injury after the use of alirocumab 1 day before PCI. According to ALPEHEUS study,[9] PCI-related MI or major myocardial injury was observed in 35% patients undergoing elective PCI. In accordance with ALPHEUS study, our previous studies also observed the similar incidence of postoperative hs-cTn elevating above 5×99 th percentile URL using the same hs-cTn assay as APPEASE trial.[15 16] Therefore, we assume the occurrence of primary endpoint without the use of alirocumab will be 35%. Data from FOURIER trial[31] showed that long-term use of PCSK9 inhibitors significantly reduce the risk of type 4a MI by 35%. But there was still lack of data focusing on the effect in type 4a MI by short-term use of PCSK9 inhibitor before PCI. As the incidence of PCI-related MI or major myocardial injury in our study is much higher than the incidence of type 4a MI in FOURIER trial, we hypothesised a 40% relative risk reduction of the primary endpoint will be effectively. Considering a total event rate for the primary endpoint of 35%, we calculated that 160 patients/group could have an 80% power to detect a 40% reduction of the occurrence of PCI-related MI or major myocardial injury after the use of alirocumab 1 day before PCI (corresponding to 56 events cases in control group and 34 events cases in alirocumab group), assuming an SD of 0.05 and at a two-sided significance level of 0.05. Based on previous studies[32] and our preliminary results, we consider the

probability that included patients eventually undergo PCI implanting drug-eluting stents will be approximately 80% in our study according to the inclusion criteria. Taking into account, an estimated drop-out rate of other reasons will be approximately 5%, 211 patients/arm for a total of 422 patients will be required in the study.

Data will be analysed from the intention-to-treat population. All data will be presented as percentages (categorical variables) or means±SD (continuous variables). The comparison of baseline data will be performed using the χ^2 test for categorical variables and Student's t-test for continuous variables. The primary and secondary endpoints including different elevation of postoperative hs-cTn (5×99 th percentile URL, and 1×99 th percentile URL to 70×99 th percentile URL) will be compared by χ^2 test between groups as described in the protocol. Univariate and multivariate cox proportional hazard regression analyses will be performed using all potentially relevant variables to compared the MACE occurrence between groups. P value 0.05 will be considered to indicate statistical significance. All statistical analyses will be performed using the SPSS software (V.26.0; SPSS).

DISCUSSION

The APPEASE trial is designed to evaluate the efficacy of additional preprocedural use of alirocumab on preventing PCI-related MI and major myocardial injury in patients with CHD undergoing elective PCI. Definition of PCI-related MI and major myocardial injury is hs-cTn elevating above 5×99 th percentile URL within 48 hours after PCI according to ESC/EAPCI Consensus Document, which have been demonstrated leading to poor prognosis in patients with CHD after PCI.[6] We also evaluate the alirocumab effect on reducing different degree of PCI-related periprocedural myocardial injury reflecting in different hs-cTn elevation within 48 hours after PCI. In addition, we will explore the effect of alirocumab on improving the short-term prognosis in patients with PCI-related MI or major myocardial injury. To our knowledge, this will be the first clinical trial specially focusing on the alirocumab effect in prevention and improvement of periprocedural ischaemic events in stable patients with CHD undergoing elective PCI.

The managements for periprocedural myocardial injury and type 4a MI have been consistently explored for decades. Adequate dose of dual anti-platelet therapy (aspirin combining clopidogrel or aspirin combining ticagrelor) are necessary before PCI.[7] High-dose statins prior to PCI was shown to be effective in reducing the risk of periprocedural myocardial injury and type 4a MI.[8] However, in ALPHEUS study, the incidence of PCI-related MI or major myocardial injury still exceeded 35% even receiving adequate dose of dual anti-platelet therapy and statins.[9] COLCHICINE-PCI trial focusing on the effectiveness of anti-inflammatory therapy in PCI showed high-dose colchicine prior to PCI for stable patients with CHD failed to reduce the incidence of type 4a MI and periprocedural myocardial injury.[33] Therefore, we perform APPEASE trial with the hope that alirocumab would reduce the occurrence of major periprocedural myocardial injury and type 4a MI, thereby improving the outcome of PCI.

Additionally, as mentioned above, PCI-related major periprocedural myocardial injury will lead to poor prognosis. As recommended in guidelines, stable patients with CHD diagnosed with major periprocedural myocardial injury should be optimised pharmacotherapy to reduce risk of future MACE.[34 35] But the benefit from the additional use of secondary prevention pharmacotherapies for CHD such as ACE-inhibitors, β-blockers and PCSK9 inhibitors for prognostically relevant major periprocedural myocardial injury are still uncertain.[6] Therefore, our study will also explore whether post-PCI treatment with alirocumab can reduce MACE in stable patients with CHD experiencing type 4a MI or major periprocedural myocardial injury.

FOURIER trial[31] and ODYSSEY OUTCOMES trial[36] demonstrating the benefit of PCSK9 inhibitors in the reduction of major vascular events have partially analysed the effect of PCSK9 inhibitors in PCI-related MI. FOURIER trial showed long-term use of evolocumab reduced the risk of PCI-related MI by 35%,[31] while ODYSSEY OUTCOMES trial showed the occurrence of PCI-related MI in alirocumab group did not differ from placebo group.[36] However, these two trials included a population without planned cardiac procedures, thus the occurrence of PCI-related MI was relatively low and occasional. Furthermore, since the patients received long-term therapy of statins and PCSK9 inhibitors prior to the occurrence of PCI-related MI, the results could not rule out the benefits of lipid-lowering effect. On the contrast, our study will enrol stable patients with CHD planned to undergo elective PCI and explore the short-term effect of PCSK9 inhibitors in prevention of periprocedural ischaemic events. The results of APPEASE trial will provide important evidences for the periprocedural use of PCSK9 inhibitors in PCI. In addition, we can further confirm the extra-lipid-lowering effects of PCSK9 inhibitors, such as anti-inflammation, plaque stabilisation, improvement of endothelial function, etc.

SUMMARY

The APPEASE trial is an investigator-initiated, multicentre, prospective, randomised, parallel controlled, open-label trial enrolling a total of 422 patients with CHD undergoing elective PCI to determine the effect of alirocumab on preventing PCI-related MI or major periprocedural myocardial injury in patients with CHD undergoing elective PCI. We will also investigate whether alirocumab could improve the prognosis of patients with CHD diagnosed type 4a MI or major periprocedural myocardial injury. The results will provide reliable evidence for the periprocedural use of PCSK9 inhibitors in PCI.

Author affiliations
[1]Department of Cardiovascular Medicine, Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China

[2]Cardiology Department, First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, China
[3]NHC Key Laboratory of Assisted Circulation, Sun Yat-Sen University, Guangzhou, Guangdong, China
[4]Department of Science and Research, Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, Guangdong, China
[5]Department of Cardiology, Cardiovascular Institute of Panyu District, Guangzhou Panyu Central Hospital, Guangzhou, Guangdong, China
[6]Department of Cardiology, Second Affiliated Hospital of Guangzhou Medical University, Guangzhou, Guangdong, China

Acknowledgements The authors thank the investigators, the APPEASE Trial Team and all doctors, nurses and patients who participated in this trial.

Contributors ZH, XZ, XQ, XL and JL contributed to the conception or design of the work. ZH, XZ and SZ drafted the manuscript. YH, LY, LT, OC were responsible for the acquisition of data from each study centre. ZH, ZX, YC, BW and YL were responsible for the follow-up of the enrolled patients. YL conducted the statistical analysis. SL, QJ and LX were responsible for the analysis and interpretation of data. Critical revision of the manuscript for important intellectual content were performed by all authors. All authors agreed with the content of the article to be submitted.

Funding This study was partially supported by the National Natural Science Foundation Cultivation Project of Third Affiliated Hospital of Sun Yat-sen University (2020GZRPYQN18 to ZH), Clinical Medical Research Special Fund 'Sailing Program' of Third Affiliated Hospital of Sun Yat-sen University (QHJH202201 to YH).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
Xiaodong Zhuang http://orcid.org/0000-0001-6508-8507
Shaozhao Zhang http://orcid.org/0000-0002-3055-4851
Xinxue Liao http://orcid.org/0000-0001-7631-1866
Jinlai Liu http://orcid.org/0000-0001-8626-1874

REFERENCES

1 Giacoppo D, Colleran R, Cassese S, *et al*. Percutaneous coronary intervention vs coronary artery bypass grafting in patients with left main coronary artery stenosis: a systematic review and meta-analysis. *JAMA Cardiol* 2017;2:1079–88.
2 Valgimigli M, Frigoli E, Leonardi S, *et al*. Radial versus femoral access and bivalirudin versus unfractionated heparin in invasively managed patients with acute coronary syndrome (MATRIX): final 1-year results of a multicentre, randomised controlled trial. *Lancet* 2018;392:835–48.
3 Stone GW, Sabik JF, Serruys PW, *et al*. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. *N Engl J Med* 2016;375:2223–35.
4 Tricoci P. Consensus or controversy?: evolution of criteria for myocardial infarction after percutaneous coronary intervention. *Clin Chem* 2017;63:82–90.
5 Silvain J, Zeitouni M, Paradies V, *et al*. Procedural myocardial injury, infarction and mortality in patients undergoing elective PCI: a pooled analysis of patient-level data. *Eur Heart J* 2021;42:323–34.
6 Bulluck H, Paradies V, Barbato E, *et al*. Prognostically relevant periprocedural myocardial injury and infarction associated with percutaneous coronary interventions: a consensus document of the ESC working group on cellular biology of the heart and European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2021;42:2630–42.
7 Valgimigli M, Bueno H, Byrne RA, *et al*. ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. *Eur J Cardiothorac Surg* 2018;53:34–78.
8 Pan Y, Tan Y, Li B, *et al*. Efficacy of high-dose rosuvastatin preloading in patients undergoing percutaneous coronary intervention: a meta-analysis of fourteen randomized controlled trials. *Lipids Health Dis* 2015;14:97.
9 Silvain J, Lattuca B, Beygui F, *et al*. Ticagrelor versus clopidogrel in elective percutaneous coronary intervention (ALPHEUS): a randomised, open-label, phase 3B trial. *Lancet* 2020;396:1737–44.
10 Ricciardi MJ, Wu E, Davidson CJ, *et al*. Visualization of discrete microinfarction after percutaneous coronary intervention associated with mild creatine kinase-MB elevation. *Circulation* 2001;103:2780–3.
11 Selvanayagam JB, Porto I, Channon K, *et al*. Troponin elevation after percutaneous coronary intervention directly represents the extent of irreversible myocardial injury: insights from cardiovascular magnetic resonance imaging. *Circulation* 2005;111:1027–32.
12 Choi CJ, Haji-Momenian S, Dimaria JM, *et al*. Infarct involution and improved function during healing of acute myocardial infarction: the role of microvascular obstruction. *J Cardiovasc Magn Reson* 2004;6:917–25.
13 Fischell TA, Derby G, Tse TM, *et al*. Coronary artery vasoconstriction routinely occurs after percutaneous transluminal coronary angioplasty. A quantitative arteriographic analysis. *Circulation* 1988;78:1323–34.
14 Salloum J, Tharpe C, Vaughan D, *et al*. Release and elimination of soluble vasoactive factors during percutaneous coronary intervention of saphenous vein grafts: analysis using the percusurge guardwire distal protection device. *J Invasive Cardiol* 2005;17:575–9.
15 Huang Z-S, Zheng Z-D, Zhang J-W, *et al*. Association of major adverse cardiovascular events and cardiac troponin-I levels following percutaneous coronary intervention: a three-year follow-up study at a single center. *Eur Rev Med Pharmacol Sci* 2020;24:3981–92.
16 Huang Z, Shui X, Ling Y, *et al*. Serum lipoprotein(A) and risk of periprocedural myocardial injury in patients undergoing percutaneous coronary intervention. *Clin Cardiol* 2020;44:176–85.
17 Luo Y, Warren L, Xia D, *et al*. Function and distribution of circulating human PCSK9 expressed extrahepatically in transgenic mice. *J Lipid Res* 2009;50:1581–8.
18 Ferri N, Tibolla G, Pirillo A, *et al*. Proprotein convertase subtilisin kexin type 9 (PCSK9) secreted by cultured smooth muscle cells reduces macrophages LDLR levels. *Atherosclerosis* 2012;220:381–6.
19 Sabatine MS, Giugliano RP, Keech AC, *et al*. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;376:1713–22.
20 Sabatine MS. PCSK9 inhibitors: clinical evidence and implementation. *Nat Rev Cardiol* 2019;16:155–65.
21 Guedeney P, Giustino G, Sorrentino S, *et al*. Efficacy and safety of alirocumab and evolocumab: a systematic review and meta-analysis of randomized controlled trials. *Eur Heart J* 2019:ehz430.
22 Robinson JG, Farnier M, Krempf M, *et al*. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *N Engl J Med* 2015;372:1489–99.
23 Iannuzzo G, Gentile M, Bresciani A, *et al*. Inhibitors of protein convertase subtilisin/kexin 9 (PCSK9) and acute coronary syndrome (ACS): the state-of-the-art. *J Clin Med* 2021;10:1510.
24 Qi Z, Hu L, Zhang J, *et al*. PCSK9 (Proprotein Convertase Subtilisin/Kexin 9) enhances platelet activation, thrombosis, and myocardial infarct expansion by binding to platelet CD36. *Circulation* 2021;143:45–61.
25 Tang Y, Li S-L, Hu J-H, *et al*. Research progress on alternative non-classical mechanisms of Pcsk9 in Atherosclerosis in patients with and without diabetes. *Cardiovasc Diabetol* 2020;19:33.
26 Li H, Wei Y, Yang Z, *et al*. Safety, tolerability, pharmacokinetics, and pharmacodynamics of Alirocumab in healthy Chinese subjects: a randomized, double-blind, placebo-controlled, ascending single-dose study. *Am J Cardiovasc Drugs* 2020;20:489–503.
27 Leucker TM, Gerstenblith G, Schär M, *et al*. Evolocumab, a PCSK9-Monoclonal antibody, rapidly reverses coronary artery endothelial dysfunction in people living with HIV and people with dyslipidemia. *J Am Heart Assoc* 2020;9:e016263.
28 Maulucci G, Cipriani F, Russo D, *et al*. Improved endothelial function after short-term therapy with evolocumab. *J Clin Lipidol* 2018;12:669–73.
29 Bernelot Moens SJ, Neele AE, Kroon J, *et al*. PCSK9 monoclonal antibodies reverse the pro-inflammatory profile of monocytes in familial hypercholesterolaemia. *Eur Heart J* 2017;38:1584–93.
30 Section of Interventional Cardiology of Chinese Society of Cardiology of Chinese Medical Association, Specialty Committee on Prevention and Treatment of Thrombosis of Chinese College of Cardiovascular Physicians, Editorial Board of Chinese Journal of Cardiology. Chinese

guideline for percutaneous coronary Intervention(2016). *Zhonghua Xin Xue Guan Bing Za Zhi* 2016;44:382–400.
31 Wiviott SD, Giugliano RP, Morrow DA, *et al*. Effect of Evolocumab on type and size of subsequent myocardial infarction: a prespecified analysis of the FOURIER randomized clinical trial. *JAMA Cardiol* 2020;5:787–93.
32 Genders TSS, Steyerberg EW, Alkadhi H, *et al*. A clinical prediction rule for the diagnosis of coronary artery disease: validation, updating, and extension. *Eur Heart J* 2011;32:1316–30.
33 Shah B, Pillinger M, Zhong H, *et al*. Effects of acute colchicine administration prior to percutaneous coronary intervention: COLCHICINE-PCI randomized trial. *Circ Cardiovasc Interv* 2020;13:e008717.
34 Knuuti J, Wijns W, Saraste A, *et al*. ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J* 2020;41:407–77.
35 Neumann F-J, Sousa-Uva M, Ahlsson A, *et al*. ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;40:87–165.
36 White HD, Steg PG, Szarek M, *et al*. Effects of alirocumab on types of myocardial infarction: insights from the ODYSSEY OUTCOMES trial. *Eur Heart J* 2019;40:2801–9.