Effects of intensive lipid lowering compared with moderate-intensity lipid lowering on coronary atherosclerotic plaque phenotype and major adverse cardiovascular events in adults with low to intermediate 10-year ASCVD risk (ILLUMINATION study): protocol for a multicentre, open-label, blinded-endpoint, randomised controlled trial

Jianan Zheng,1 Zhihui Hou,1 Jinqing Yuan,2 Xueyan Zhao,2 Yang Wang,3 Jia Li,2 Wenjia Zhang,2 Kefei Dou1,2 Bin Lu1

ABSTRACT

Introduction Current guidelines recommend moderate-intensity lipid lowering (low-density lipoprotein cholesterol, LDL-C of <2.6 mmol/L or 30%–49% reduction from the baseline) for patients with intermediate 10-year atherosclerotic cardiovascular disease (ASCVD) risk. The effects of intensive lipid lowering (LDL-C of <1.8 mmol/L) on coronary atherosclerotic plaque phenotype and major adverse cardiovascular events (MACE) in adults with both non-obstructive coronary artery disease (CAD) and low to intermediate 10-year ASCVD risk remain uncertain.

Methods and analysis Intensive Lipid-lowering for Plaque and Major Adverse Cardiovascular Events in Low to Intermediate 10-year ASCVD Risk Population is a multicentre, randomised, open-label, blinded-endpoint clinical trial. Inclusion criteria are as follows: (1) patients with the age of 40–75 years within 1 month of coronary CT angiography (CCTA) and coronary artery calcium score (CACS) evaluation; (2) population with low to intermediate 10-year ASCVD risk (<20%) and (3) patients with non-obstructive CAD (stenosis <50%) using CCTA. 2900 patients will be randomly assigned to the intensive lipid lowering (LDL-C of <1.8 mmol/L or ≥50% reduction from the baseline) or the moderate-intensity lipid lowering (LDL-C of <2.6 mmol/L or 30%–49% reduction from the baseline) group in a 1:1 ratio. The primary endpoint is MACE (composite of all-cause death, non-fatal MI, non-fatal stroke, any revascularisation and hospitalisation for angina) within 3 years after enrolment. The secondary endpoints are changes in coronary total plaque volume (mm³), plaque burden (%), plaque composition (mm³, %), high-risk plaque characteristics detected using CCTA and CACS determined using CT.

Ethics and dissemination Ethics committee approval for this study was obtained from the review boards of Fuwai Hospital (No.2022-1787) and all other study sites. Written informed consent will be obtained from all participants. The results of this study will be published in peer-reviewed journals and reported at international conferences.

Trial registration number NCT05462262.

INTRODUCTION

Lowering lipids is very important in preventing atherosclerosis and thus, primary atherosclerotic cardiovascular diseases (ASCVDs), including coronary artery disease (CAD), stroke and peripheral vascular disease. The 2019 ACC/
AHA (the American College of Cardiology and American Heart Association) guidelines on the primary prevention of cardiovascular disease and the 2019 ESC/EAS (the European Society of Cardiology and European Atherosclerosis Society) guidelines for the management of dyslipidaemias recommended moderate-intensity lipid-lowering therapy (achieving an low-density lipoprotein cholesterol (LDL-C) of <2.6 mmol/L or a 30%–49% reduction of LDL-C from the baseline) for the primary prevention of ASCVDs in the population at 10-year ASCVD borderline and intermediate risk. Nevertheless, current guidelines advocate lipid-lowering therapy for the primary prevention of ASCVD based on clinical risk stratification. With the increased use of non-invasive tests in determining cardiovascular diseases in clinical practices, the application of risk-enhancing factors, besides clinical risk factors, detected by non-invasive tests remains to be explored. 

Coronary CT angiography (CCTA) produces accurate images of early coronary atherosclerotic lesions and provides a wealth of anatomical and functional attributes, including plaque burden (total plaque volume, calcification score and segment involvement score), plaque composition, characteristics of high-risk plaque, luminal stenosis and CCTA-derived fractional flow reserve. Complete CCTA imaging-based information is used in risk stratification, guiding primary prevention of ASCVD and predicting major adverse cardiovascular events (MACEs) in non-obstructive CAD patients.

Statin therapy reduced myocardial infarction (MI) and adverse events through primary prevention and secondary prevention interventions. Combining ezetimibe with statin also reduced the risk of MACE in patients, demonstrating the incremental benefits when adding other lipid-lowering drugs. In statin-intolerant patients, treatment with bempedoic acid could be considered for further LDL-C reduction, which was demonstrated to reduce the risk of MACE. In a previous study by Øvrehus et al, the benefit of statin treatment in the primary prevention of CAD was directionally proportional to CAD burden. Regarding different clinical risk stratifications, a study published in the New England Journal of Medicine demonstrated that a moderate-intensity statin therapy resulted in significantly lower adverse cardiovascular events than a placebo in intermediate-risk patients without cardiovascular disease. However, heterogeneity in the extent of coronary atherosclerosis exists in patients with low to intermediate risk, and CCTA imaging could differentiate these differences. Combining clinical risk stratification and CCTA findings in making precise risk re-stratification and primary prevention intervention, is presently lacking. Therefore, this study aims to use CCTA in exploring better strategies for the primary prevention of ASCVD. We predict that intensive lipid lowering in adults with low to intermediate 10-year ASCVD risk and non-obstructive CAD determined by CCTA will improve clinical outcomes compared with moderate-intensity lipid lowering.

**METHODS AND ANALYSIS**

**Study design**

Intensive Lipid-lowering for Plaque and Major Adverse Cardiovascular Events in Low to Intermediate 10-year ASCVD Risk Population (ILLUMINATION; NCT05462262) is a prospective, randomised, open-label, blind endpoint clinical trial being conducted at 28 clinical centres in China. Recruitment will be competitive with no maximum limit for the patient from each centre. The onset of the enrollment was on 10 October 2022. The estimated end of the enrolment will be on 31 October 2023. A core laboratory will be responsible for image analysis, interpretation and quality control. The flow chart of the ILLUMINATION study is shown in figure 1.

**Study objectives**

The primary objective is to determine whether intensive lipid lowering could reduce the incidence of MACE in patients with non-obstructive CAD and low to intermediate 10-year ASCVD risk, compared with moderate-intensity lipid lowering. The secondary objectives are to compare the effects of intensive lipid lowering versus moderate-intensity lipid lowering on the plaque phenotype determined using CCTA.

**Patient population**

The study population includes patients between 40 and 75 years of age within 1 month of CCTA imaging and coronary artery calcium score (CACS) scan. The inclusion criteria are as follows: (1) population with low to intermediate 10-year ASCVD risk of <20% calculated using pooled cohort equations and (2) patients with non-obstructive CAD (stenosis of <50%) diagnosed on CCTA.

The exclusion criteria are as follows:

1. Patients who have comorbidities, such as serious cardiovascular diseases, including heart failure (ejection fraction of <30%), arrhythmias (persistent atrial flutter/atrial fibrillation and second-degree or third-degree atrioventricular block), haemodynamically important valvular disease, haemodynamically important congenital heart disease and stroke.
2. Patients with MI, coronary revascularisation or severe/unstable angina before or within 1 month of screening.
3. Patients with active liver disease or hepatic dysfunction (determined from alanine aminotransferase or aspartate aminotransferase level of >3 times the upper limit of normal).
4. Patients with unexplained creatine phosphokinase levels of >6 times the upper limit of normal.
5. Patients with nephrotic syndrome.
6. Patients with diabetes mellitus.
7. Patients with uncontrollable hypertension.
8. Patients with uncontrollable hypothyroidism.
9. Patients who are hypersensitive to statins.
11. Patients with gastrointestinal diseases affecting drug absorption or a history of gastrointestinal surgery.
12. Patients with survival-limiting diseases.
13. Patients who have concurrent long-term immunosuppressive therapy.
14. Patients participating in another clinical trial concurrently or within 30 days before screening.
15. Patients who are pregnant or breast feeding.
16. Patients who are unable to give informed consent.
17. Patients with other unsuitable situations that are deemed by physicians.

**Intervention and follow-up**

Eligible patients will be randomised into the intervention group (LDL-C of <1.8 mmol/L or ≥50% reduction from the baseline) and control group (goal for LDL-C of <2.6 mmol/L or 30%-49% reduction from baseline, according to current guidelines for ASCVD primary prevention) in a 1:1 ratio using computer-generated random allocation. The LDL-C values will be controlled to the target levels through lipid-lowering therapy and/or lifestyle modification in patients in both groups. The lipid-lowering therapies include statins, ezetimibe and proprotein convertase subtilisin/kexin type 9 inhibitors. Based on the tolerance in Chinese people, statin therapy will be started at a moderate intensity. If the target of LDL-C is not achieved in 1 month, the statin dose will be increased appropriately, or ezetimibe will be added. If the therapy still does not achieve the goal within 6 months, a proprotein convertase subtilisin/kexin type 9 inhibitor will be considered to lower the lipids. However, the type, dose and combinatory drugs need to be tailored to individual patients by physicians. Following dispensing of the study drug and/or giving healthy lifestyle recommendations, randomised patients will be clinically evaluated at 1, 3 and 6 months and then every 6 months thereafter. Within 6 months of randomisation, lipid-lowering therapy will be adjusted based on the treatment effect. Follow-up LDL-C values will be reported to the patients and physicians to adjust the drug regimen to ensure differences between the control and intervention groups. Patients will be clinically evaluated within 6 weeks after each adjustment of medication for efficacy and adverse drug reactions. Follow-up CCTA and CACS will be performed after about 3 years. MACE will be followed up for about 3 years. The details of the follow-up procedure are shown in online supplemental table 1.

**Study endpoints**

The primary endpoint is the incidence rate of MACE, and the secondary endpoints are the change in plaque burden, plaque composition, high-risk plaque characteristics and plaque progression determined using CCTA and CACS by CT. The details of study endpoints and definitions are shown in box 1.

**Sample size and statistical analysis**

All the statistical analyses will be performed using SPSS V.22.0 for Windows (SPSS) by an expert in medical statistics. For descriptive analysis, continuous variables will be represented as the mean±SD, and categorical variables will be presented as percentages. Categorical variables will be compared using χ² statistics and continuous
variables will be compared using a t-test. We will test the interobserver agreement of CCTA variables by k-statistic. Cumulative event rates as stratified by intervention and the control group will be estimated using the product limit (Kaplan-Meier) methods and the log-rank test. A two-sided p<0.05 will be considered to indicate statistical significance.

According to 2012 literature, the incidence of 3-year MACE events in outpatients with non-obstructive coronary heart disease was 3.7%. It is expected that enhanced lipid-lowering will reduce the 3-year MACE events to 1.8%, which is a clinically acceptable positive cut-off value. The two-sided statistical significance level is 0.05, and the confidence level is 80%. The sample size (N1) in the intensive intervention group=the sample size (N2) in the control group=1160. It is increased to 1450 in each group to account for a 20% loss during follow-up. A total sample size of 2900 patients is required.

**Patient and public involvement**

None.

**ETHICS AND DISSEMINATION**

The study adheres to the principles of the Declaration of Helsinki and the specifications of the International Conference on Harmonisation, and Good Clinical Practice. Ethics committee approval for this study was obtained from the Fuwai Hospital Institutional Review Board (No.2022-1787) and the institutional review boards/institutional ethics committees at all other sites. Written and verbal informed consent will be provided by all patients (see online supplemental material for consent form). This trial is an investigator-initiated study with financial support from the Chinese Academy of Medical Sciences and Peking Union Medical College. The study has set up a management committee, an endpoints committee and a third-party independent imaging reading centre to ensure smooth progress. All completed electronic case report forms from each of the 28 sites will be collected from the Electronic Data Capture System (https://edc.fuwai.cn/reports) and transmitted to a central data repository to generate the master ILLUMINATION dataset. All study-related information will be stored securely at the study site. The third-party independent imaging reading centre is responsible for interpreting images and quality control. The results of this study will be published in peer-reviewed journals and reported at international conferences.

**DISCUSSION**

The ILLUMINATION study is the first randomised controlled trial to use the CCTA imaging information as a risk-enhancing factor in evaluating the effects of intensive lipid lowering in the primary prevention of ASCVD. Unlike previous studies, this trial uses LDL-C targets for grouping patients and interventions, which is more aligned with real-world primary prevention strategies. The outcomes due to intensive lipid lowering will be both evaluated using both plaque phenotype and MACE to elucidate the development and prognosis of atherosclerosis. However, this is an open-label and assessor-blinded trial, and the patients and physicians will not be blinded to the randomisation. Further, the study will not strictly follow the types of lipid-lowering drugs or lifestyle changes recommended to patients, which may introduce some confounding effects.

Many previous studies found that lowering lipids by statin therapy prevented coronary atherosclerotic plaque progression. Statin therapy reduced the total plaque burden, diminished plaque volume progression and attenuated the characteristics of high-risk plaque. Statin transformed atherosclerotic plaque compositions towards high-density calcium. In addition, a systematic review and meta-analysis by Andelius et al showed that statin therapy reduced non-calcified plaque volume and low-attenuation plaque volume but increased calcified plaque volume and calcium signal intensity. Intensive statin therapy showed more pronounced effects than moderate statin therapy. Studies that used optical coherence tomography found more effects from intensive statin therapy on plaque phenotypes, such as an increase of minimum fibrous cap thickness, reduction of macrophage accumulation and regression of thin cap fibroatheroma. Besides statin therapy, intensive lifestyle interventions had benefits in slowing plaque progression and reducing non-calcified plaque volume in non-obstructive CAD. Although there are many studies of statin therapy and...
coronary atherosclerotic plaque, allocating statin dosages and selecting lipid-lowering target values for the primary prevention of ASCVD based on CCTA remains unknown.

Previous studies of cholesterol lowering mostly focused on secondary prevention and were drug-based randomised controlled trials, neglecting early prevention of atherosclerotic lesions and accurate stratification based on non-invasive imaging tools. In contrast to the previous studies, the ILLUMINATION study identifies early coronary atherosclerotic lesions detected by CCTA for early primary prevention using drugs and intervention by adopting a healthy lifestyle, thereby delaying plaque progression and reducing the risk of long-term MACE, thus achieving complete prevention of early disease.

The ILLUMINATION study is designed to address the question of whether intensive lipid lowering further delays plaque progression and reduces MACE compared with moderate-intensity lipid lowering in adults with low to intermediate 10-year ASCVD risk. When results are available, more information on the effects of lipid lowering will be provided on coronary atherosclerotic plaque phenotype and adverse cardiovascular events in primary prevention. If a clinically worthwhile benefit is detected, the ILLUMINATION study is expected to provide new insights into CCTA-based detection and prevention of early coronary atherosclerotic lesions and further risk stratification to reduce the risk of MACE in patients with non-obstructive CAD.

Author affiliations
1Department of Radiology, Fuwai Hospital, National Centre for Cardiovascular Diseases, National Clinical Research Centre for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College/ National Center for Cardiovascular Diseases, Beijing, China
2Department of Cardiology, Fuwai Hospital, National Centre for Cardiovascular Diseases, National Clinical Research Centre for Cardiovascular Diseases, Chinese Academy of Medical Sciences & Peking Union Medical College/ National Center for Cardiovascular Diseases, Beijing, China
3Medical Research & Biometrics Center, National Center for Cardiovascular Diseases, Beijing, China

Contributors
Conception and design of the study: BL, ZH and JZ. Methodology: JY and XZ. Acquisition of data: JL and WZ. Analysis of data: YW. Writing—original draft, tables and figures: JZ. Writing—reviewing and editing: BL and ZH. Funding acquisition: KD and BL. All authors approved the final version of the manuscript.

Funding
This study is supported by the Chinese Academy of Medical Sciences and Peking Union Medical College (grant number: 2021-I2M-1-008).

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.

Supplemental material
This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminologies, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

REFERENCES
