Official Protocol Title:	A Phase 3 Randomized, Active-Comparator-Controlled Clinical Study to Evaluate the Efficacy and Safety of Ezetimibe/Atorvastatin Combination Tablet (MK-0653C) as Second Line Lipid Lowing Treatment in Chinese Participants
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Title Page

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Protocol Title: A Phase 3 randomized, active-comparator-controlled clinical study to evaluate the efficacy and safety of Ezetimibe/Atorvastatin combination tablet (MK-0653C) as second line lipid lowing treatment in Chinese participants

Protocol Number: 439-00

Compound Number: MK-0653C

Sponsor Name:

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or MSD)

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Regulatory Agency Identifying Number(s):

Approval Date: 05-November-2018

Sponsor Signatory

Typed Name:
Title:

Date

Protocol-specific Sponsor contact information can be found in the Investigator Study File Binder (or equivalent).

Investigator Signatory

I agree to conduct this clinical study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol.

Typed Name:
Title:

Date

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1 PROTOCOL SUMMARY

1.1 Synopsis

Protocol Title: A Phase 3 randomized, active-comparator-controlled clinical study to evaluate the efficacy and safety of Ezetimibe/Atorvastatin combination tablet (MK-0653C) as second line lipid lowing treatment in Chinese participants

Short Title: MK-0653C vs. atorvastatin in Chinese hypercholesterolemic participants

Acronym: MK0653C-439

Hypotheses, Objectives, and Endpoints:

All objectives and hypotheses will be evaluated in Chinese participants with hypercholesterolemia, inadequately controlled with 10 mg or 20 mg atorvastatin monotherapy.

Objectives	Endpoints
Primary	
• Objective: To evaluate the percent change in LDL-C from baseline to Week 12 of MK-0653C 10/10 mg compared to atorvastatin 20 mg (Cohort A). Hypothesis: MK-0653C 10/10 mg is superior to atorvastatin 20 mg (Cohort A) in percent change from baseline in LDL-C to 12 weeks after treatment. • Objective: To evaluate the percent change in LDL-C from baseline to Week 12 of MK-0653C 10/20 mg compared to atorvastatin 40 mg (Cohort B). Hypothesis: MK-0653C 10/20 mg is superior to atorvastatin 40 mg (Cohort B) in percent change from baseline in LDL-C to 12 weeks after treatment. Overall success is determined by a success on at least one hypothesis.	• Low-Density Lipoprotein – Cholesterol (LDL-C) level

Objectives	Endpoints
Secondary	
• Objective: To evaluate the safety and tolerability of administrated MK-0653C 10/10 mg and MK-0653C 10/20 mg once daily dosing through 12 weeks.	• Adverse events • Laboratory parameters and vital signs • Study drug discontinuation

Overall Design:

Study Phase	Phase 3
Primary Purpose	Treatment
Indication	Hypercholesterolemia
Population	Chinese participants with hypercholesterolemia inadequately controlled by 10 mg or 20 mg atorvastatin.
Study Type	Interventional
Intervention Model	Parallel This is a multi-site study.
Type of Control	Active Control Without Placebo
Study Blinding	Double-blind with in-house blinding
Masking	Participant or Subject Investigator Monitor
Estimated Duration of Study	The Sponsor estimates that the study will require approximately 1.5 years from the time the first participant signs the informed consent until the last participant's last study-related telephone call or visit.

Number of Participants:

Approximately 450 participants will be randomized across two cohorts defined by statin dose at the screening visit. In Cohort A (atorvastatin ≤10 mg or equivalent), 180 participants will be randomized, and in Cohort B (atorvastatin 20 mg or equivalent), 270 participants will be randomized.

Intervention Groups and Duration:

Intervention Groups

During double-blinded treatment period:

Intervention Group Name	Drug	Dose Strength	Dose Frequency	Route of Admin.	Regimen/ Treatment Period	Use
A1	MK-0653C FDC (ezetimibe 10 mg + atorvastatin 10 mg)	10 mg/ 10 mg	QD	Oral	Randomization treatment: 12 weeks	Study treatment
	Placebo atorvastatin	0 mg	QD	Oral	Randomization treatment: 12 weeks	Dummy with study treatment
A2	atorvastatin	20 mg	QD	Oral	Randomization treatment: 12 weeks	Active control
	Placebo of MK-0653C FDC (ezetimibe 10 mg + atorvastatin 10 mg)	0 mg	QD	Oral	Randomization treatment: 12 weeks	Dummy with active control
B1	MK-0653C FDC (ezetimibe 10 mg + atorvastatin 20 mg)	10 mg/ 20 mg	QD	Oral	Randomization treatment: 12 weeks	Study treatment
	Placebo of atorvastatin	0 mg	QD	Oral	Randomization treatment: 12 weeks	Dummy with study treatment
B2	atorvastatin	20 mg x 2	QD	Oral	Randomization treatment: 12 weeks	Active control
	Placebo of MK-0653C FDC (ezetimibe 10 mg+ atorvastatin 20 mg)	0 mg	QD	Oral	Randomization treatment: 12 weeks	Dummy with active control

Total Number	4
Duration of Participation	Each participant will participate in the study for approximately 21 weeks, from the time the participant signs the Informed Consent Form (ICF) through the final contact. After a screening phase of 2 weeks followed by an atorvastatin treatment period of approximately 5 weeks, each participant who has not met treatment target criteria will receive assigned intervention for approximately 12 weeks. After the end of treatment each participant will be followed for 14 days.

Study Governance Committees:

Steering Committee	No
Executive Oversight Committee	No
Data Monitoring Committee	No
Clinical Adjudication Committee	No
Study governance considerations are outlined in Appendix 1.	

Study Accepts Healthy Volunteers: No

A list of abbreviations used in this document can be found in Appendix 8.

1.2 Schema

The study design is depicted in Figure 1.

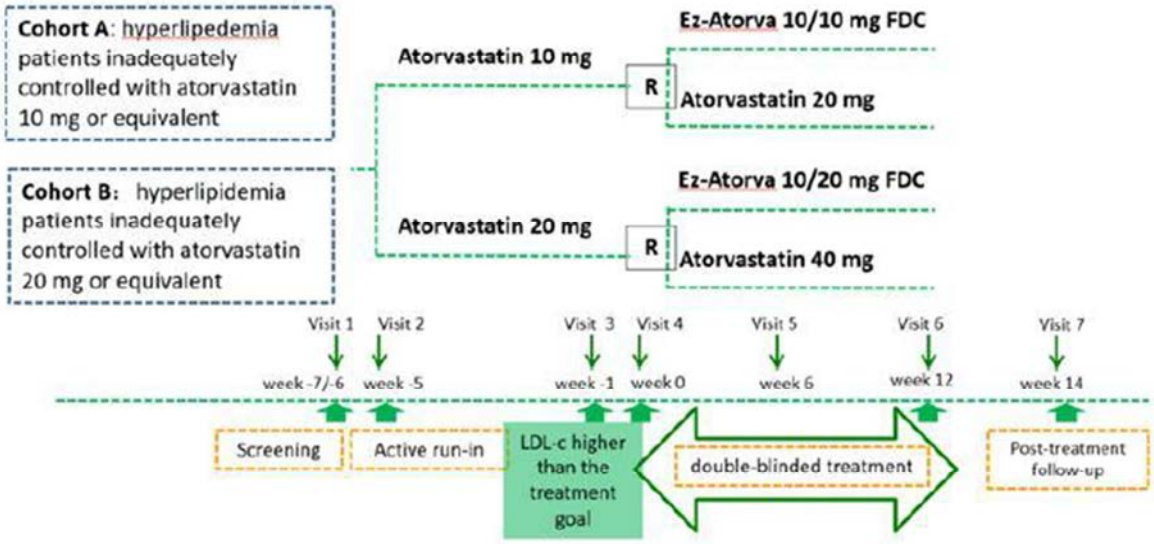

Figure 1 Study Design

1.3 Schedule of Activities (SoA)

Study Period	Screening	Active run-in period (5 weeks)		Treatment (12 weeks)			Follow-up (14 days post last dose)	Notes
Visit Number/Title	Visit 1/ Screening	Visit 2	Visit 3	Visit 4/ baseline	Visit 5	Visit 6/ Discontinuation	Phone call	
Scheduled Hour, Day, Week, etc., and Window:	Week -7/-6	Week -5 (±7 days)	Week -1 (+3 days)	Week 0 (±3 days)	Week 6 (±7 days)	Week 12 (±7 days)	±3 days	The dates of Visit 3 and Visit 4 will be decided based on the date of Visit 2, while the dates of Visit 5 & Visit 6 will be decided based on the date of Visit 4.
Administrative Procedures								
Informed Consent	X							
Inclusion/Exclusion Criteria	X			X				
Participant Identification Card	X							The card will be updated once randomized.
Medical History	X							
Prior/Concomitant Medication Review	X	X	X	X	X	X		
Assignment of Screening Number	X							
LDL-C treatment target evaluation based on Cardiac Risk assessment	X							Based on Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (2016 Edition).
Monitor Dietary/Exercise Compliance	X	X	X	X	X	X		
Monitor Medication Compliance			X	X	X	X		
Assignment of Treatment/Randomization number				X				

Study Period	Screening	Active run-in period (5 weeks)		Treatment (12 weeks)			Follow-up (14 days post last dose)	Notes
Visit Number/Title	Visit 1/ Screening	Visit 2	Visit 3	Visit 4/ baseline	Visit 5	Visit 6/ Discontinuation	Phone call	
Scheduled Hour, Day, Week, etc., and Window:	Week -7/-6	Week -5 (±7 days)	Week -1 (+3 days)	Week 0 (±3 days)	Week 6 (±7 days)	Week 12 (±7 days)	±3 days	The dates of Visit 3 and Visit 4 will be decided based on the date of Visit 2, while the dates of Visit 5 & Visit 6 will be decided based on the date of Visit 4.
Run-in atorvastatin administration/dispensing		X						
MK-0653C/ Atorvastatin + matching placebo administration/dispensing				X	X			
Efficacy Procedures								
Lipid Panel A	X		X	X	X	X		LDL-C, total cholesterol (TC), HDL-C, non-HDL-C, and Triglyceride (TG). Blood sample should be drawn after at least 10-hour fasting. Otherwise the visit need to be rescheduled. Result of local lab within 4 weeks prior to Visit 1 can be used as reference for participant screening.
Apo protein (Apo) B				X	X	X		Blood sample should be drawn after at least 10-hour fasting. Otherwise the visit needs to be rescheduled.
Safety Procedures								
Full Physical Examination including height and weight	X			X		X		

Study Period	Screening	Active run-in period (5 weeks)		Treatment (12 weeks)			Follow-up (14 days post last dose)	Notes
Visit Number/Title	Visit 1/ Screening	Visit 2	Visit 3	Visit 4/ baseline	Visit 5	Visit 6/ Discontinuation	Phone call	
Scheduled Hour, Day, Week, etc., and Window:	Week -7/-6	Week -5 (±7 days)	Week -1 (+3 days)	Week 0 (±3 days)	Week 6 (±7 days)	Week 12 (±7 days)	±3 days	The dates of Visit 3 and Visit 4 will be decided based on the date of Visit 2, while the dates of Visit 5 & Visit 6 will be decided based on the date of Visit 4.
Vital Signs (heart rate, blood pressure)	X	X	X	X	X	X		
12-lead ECG	X							ECG will performed locally and results should be checked and confirmed by the investigator or qualified designee.
Urine/ Serum β-Human Chorionic Gonadotropin (β-hCG; WOCBP only)	X			X	X	X		Serum β-hCG test is determined by central lab if urine pregnancy performed at the site is positive.
fT4 and TSH	X							Result of local lab within 4 weeks prior to Visit 1 can be used as reference for participant screening.
Hematology	X			X		X		Result of local lab within 4 weeks prior to Visit 1 can be used as reference for participant screening.
Urinalysis	X			X		X		Result of local lab within 4 weeks prior to Visit 1 can be used as reference for participant screening.

Study Period	Screening	Active run-in period (5 weeks)		Treatment (12 weeks)			Follow-up (14 days post last dose)	Notes
Visit Number/Title	Visit 1/ Screening	Visit 2	Visit 3	Visit 4/ baseline	Visit 5	Visit 6/ Discontinuation	Phone call	
Scheduled Hour, Day, Week, etc., and Window:	Week -7/-6	Week -5 (±7 days)	Week -1 (+3 days)	Week 0 (±3 days)	Week 6 (±7 days)	Week 12 (±7 days)	±3 days	The dates of Visit 3 and Visit 4 will be decided based on the date of Visit 2, while the dates of Visit 5 & Visit 6 will be decided based on the date of Visit 4.
Chemistry	X		X	X	X	X		Blood sample should be drawn after at least 10-hour fasting. Otherwise the visit need to be rescheduled. Result of local lab within 4 weeks prior to Visit 1 can be used as reference for participant screening.
AE/SAE Monitoring	X	X----------X						The serious adverse events occurred within 14 days after last study drug administration must be reported to Sponsor.

2 INTRODUCTION

Atherosclerosis has traditionally been regarded as a disease primarily characterized by the progressive fatty debris in the arterial wall followed by progressive stenosis, and consequently rupture of this plaque, resulting in occlusive thrombosis and eventually cause life-threatening heart attack, stroke and so on. Dyslipidemia characterized by the increase of low-density lipoprotein cholesterol (LDL-C) or TC is an important risk factor for atherosclerotic cardiovascular diseases. Over the last 30 years, the blood lipid level in the Chinese population has gradually increased, and the incidence of dyslipidemia has significantly increased [Moran, A., et al 2010], accompanied by a significant change in disease profile: coronary heart disease became the most predominant heart disease.

The reduction of LDL-C levels can significantly decrease the development and mortality risks of atherosclerotic cardiovascular diseases which were already proved by great lot of evidences since landmark 4S trial. The analytic results of the Cholesterol Treatment Trial indicate that 1 mmol/L LDL-C reduction by statin therapy in populations with different cardiovascular risk stratifications can produce a 20% the relative risk reduction of major cardiovascular events and 10% risk reduction of all-cause mortality, whereas the mortality caused by non-cardiovascular reasons does not increase. Meta-analyses and epidemiology studyies have shown that the reduction in CHD risk is proportional to the absolute change in LDL-C, i.e., greater reductions of LDL-C lead to greater cardiovascular risk reductions [Stamler, J., et al 1986] [Chen, Z., et al 1991] [Szatrowski, T. P., et al 1984] [Gould, A. L., et al 1998].

Statin was proved to be a potent LDL-C lowing agent and was widely used in primary prevention and secondary prevention of CV event. However, doubling statin dose did not correspond to a doubled LDL-C reduction. Introduction of other lipid lowing agents can provide greater LDL-C reduction when added to a statin and was recommended by local guideline. Ezetimibe provides greater improvements in lipid profile and goal attainment when added to a statin compared to a statin monotherapy [Stein, E., et al 2004] [Goldberg, A. C., et al 2004] [Pearson, T. A., et al 2005] [US Prescribing Information 2013] [UK Summary of Product Characteristics 2013].

Cumulatively, there were approximately 1,038,850 patient-years of treatment with ezetimibe/atorvastatin, of which approximately 2875 subjects treated with ezetimibe/ atorvastatin fixed dose combination, and approximately 3,252 subjects treated with coadministered ezetimibe (+) atorvastatin in Marketing Authorization Holder-sponsored clinical trials. Data from trials and experience of co-administration provide the largest body of efficacy and safety data for the FDCs. And 2 definitive bioequivalence studies established the comparability between the FDC and the corresponding individual ezetimibe and atorvastatin tablets when co-administered [Ballantyne, C. M., et al 2005] [Catapano, A., et al 2005].

Based on the favorable efficacy and risk profile of co-administration of atorvastatin and ezetimibe and the proved bioequivalent of FDC to co-administration of atorvastatin and ezetimibe, MK-0653C has been approved in 49 countries by the time of Feb 2018.

2.1 Study Rationale

This trial is designed to demonstrate the superiority of MK-0653C (Ezetimibe/Atorvastatin combination tablet) 10/10 mg or 10/20 mg compare to a doubling dose of atorvastatin in LDL-C lowing effect in hypercholesterolemia participants not well controlled by statin monotherapy. The data from this trial will support the market authorization in China.

2.2 Background

MK-0653C is a fixed dose combination drug containing ezetimibe, a Niemann-Pick Cl Like 1 (NPC1L1) inhibitor, and atorvastatin, a HMG-CoA reductase inhibitor, as active ingredients. The active ingredients are ezetimibe 10 mg and atorvastatin 10 mg or 20 mg.

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on atorvastatin, ezetimibe and MK-0653C.

2.2.1 Pharmaceutical and Therapeutic Background

Coronary heart disease (CHD), stroke and peripheral arterial disease caused by atherosclerosis are quite significant burdens to medical care in developed and developing countries [Barquera, S., et al 2015], and these diseases have taken the leading cause of death among both urban and rural areas in China [Yang, G., et al 2013]. The number of CHD incidence and mortality is rapidly increasing in recent 20 years in China [Zhou, M., et al 2016]. Considering the rapid aging speed in China, the future medical burden related to CHD will be even more critical. Blood cholesterol and the LDL-C are the independent risk factors to the CHD and ischemic stroke in Chinese cohort studies [Ren, J., et al 2010] [Li, Q., et al 2017]. Five large clinical studies: 4S, CARE, LIPID, WOSCOPS, and AFCAPS/TexCAPS have strongly established the base for statins to treat and prevent CHD progression by lowering TC and LDL-C. The following series studies, AVERT, LIPS, HPS, PROSPER, ASCOT, PROVE-IT, TNT, and IDEAL have demonstrated the benefit of statins to even acute coronary disease and multiple subgroup risky populations. Lower LDL-C became possible and gradually target for high risk and very high risk populations.

Statins have been introduced to China, and proved their efficacy on lowering LDL-C to 18-55% among Chinese patients. However, only 6-7% more reduction can be expected when doubling the doses if the LDL-C cannot be adequately controlled after initiation of statin monotherapy. Moreover, increasing statin dose is less efficacy in lipid control while adverse events of myopathy and liver function abnormality increased with dosing, especially in Chinese patients. In order to achieve the treatment goal and to further reduce the CHD risk, new medicines are introduced to China, within whom, ezetimibe is recommended to be selected as combined medicine with statins in clinical setting in China to enhance the efficacy while no more safety or tolerability issues [IMS Health 2006] [Grundy, S. M., et al 2004]. Combination of 10 mg ezetimibe with 10 mg atorvastatin or simvastatin may increase the rate of target achievement from around 18% to 72%, and the efficacy of combination use is similar to high dose (80 mg) of atorvastatin or simvastatin [Ballantyne, C. M., et al 2003] [Davidson, M. H., et al 2002] [Mikhailidis, D. P., et al 2009]. Therefore, China guideline

highly recommends using ezetimibe with low dose of atorvastatin to gain the similar effect. It also stated that there would be no additional risks of liver toxicity, myopathy or rhabdomyolysis when combining ezetimibe with statins compared to statin alone [Ballantyne, C. M., et al 2003] [Davidson, M. H., et al 2002] [Mikhailidis, D. P., et al 2009].

Significance of the Development of Fixed Dose Combination (FDC) Tablet for Therapy of Hyper-LDL-cholesterolemia

- **Mode of action**

Ezetimibe inhibits the intestinal absorption of cholesterol and structurally-related phytosterols by blocking their passage across the intestinal wall. The molecular target of ezetimibe action has been identified as the putative cholesterol transporter NPC1L1. This blockade results in decreased absorption of dietary and biliary cholesterol without effects on the absorption of other lipids (e.g., triglyceride), lipid derivatives (e.g., bile acids) or lipidsoluble nutrients or vitamins.

Atorvastatin is a synthetic HMG-CoA reductase inhibitor. Atorvastatin and its metabolites, which show a similar level of activity, inhibit hepatic synthesis of cholesterol by selectively and competitively inhibiting HMG-CoA reductase in the liver, one of the main organs, that regulates the amount of cholesterol in the blood. As a result, atorvastatin increases the number of hepatic LDL receptors and inhibits lipoprotein secretion, thereby reducing the amount of lipids in blood [Haque, T. 2010].

Ezetimibe reduces hepatic cholesterol stores by inhibiting the absorption of cholesterol in the small intestine, but compensatory increased cholesterol biosynthesis occurs in the liver.

Coadministration of ezetimibe and an HMG-CoA reductase inhibitor which inhibits cholesterol biosynthesis was shown to complementarily lower cholesterol in studies in dogs and in hypercholesterolemic patients [Van Heek, M. and Davis, H. 2002] [Toth, P. P., et al 2010] [Grigore, L., et al 2008].

- **Adherence**

In a recent survey on adherence to statin treatment revealed a decrease in adherence with time; thus, statin treatment adherence is estimated to be about 50% in long-term therapy [Shroufi, A. 2010]. In addition, data on other diseases show that the treatment compliance rate is correlated with the number of tablets (capsules) prescribed [Ingersoll, K. S. and Cohen, J. 2008] [Cheong, C., et al 2008]. Therefore, a combination drug with a good tolerability profile in combination therapy for hyper-LDL-cholesterolemia may well be an important alternative as a treatment drug that can improve patients' treatment adherence and may be anticipated to display more reliable therapeutic efficacy. Consequently, concomitant administration of ezetimibe and statin is assumed to more effectively improve hyper-LDL-cholesterolaemia based on their different mechanisms of actions.

2.2.2 Clinical Studies

IMPROVE-IT Study

The IMPROVE-IT [Cannon, C. P., et al 2015] (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) study was a multicenter, randomized, double-blind study, designed to establish the incremental clinical benefit and safety of ezetimibe (administered as part of ezetimibe/simvastatin Combination 10/40 mg tablet, a single tablet containing ezetimibe 10 mg and simvastatin 40 mg, if a participant had 2 consecutive LDL-C measurements >79 mg/dL, then that participant was to have his/her simvastatin dose increased to 80 mg.) compared with simvastatin monotherapy in high-risk coronary artery disease participants and aims to address the question of whether the incremental reductions of LDL-C will translate into a clinical benefit. The study enrolled 18,144 high-risk participants with established coronary artery disease. At seven years, 32.7 percent of patients taking ezetimibe/Simvastatin experienced a primary endpoint event compared to 34.7 percent of patients taking simvastatin alone (hazard ratio of 0.936, p=0.016). Based on the LDL-C range compared in the study's treatment arms (at one year, a mean LDL-C of 53 mg/dL versus 70 mg/dL, respectively), the 6.4 percent relative risk reduction observed in the ezetimibe/simvastatin arm in IMPROVE-IT was consistent with the treatment effect that had been projected based on prior studies of statins.

With regard to safety, there were no significant differences between treatment groups in adverse events of special interest in the trial, which included myopathy and rhabdomyolysis, gallbladder adverse events, liver enzyme elevations greater than or equal to three times the upper limit of normal, and cancer. These safety findings from IMPROVE-IT were generally consistent with current labeling for ezetimibe.

MK-0653C Studies

Currently there are no clinical data available of combination administration of ezetimibe and atorvastatin in Chinese. However, there are clinical data globally on combination administration of ezetimibe and atorvastatin. The completed studies demonstrated the combination of ezetimibe and atorvastatin has superior LDL-C lower effect compare to the monotherapy of ezetimibe or atorvastatin. Especially in two add-on studies in patients whose LDL-C were not well controlled by atorvastatin treatment alone, adding ezetimibe 10 mg achieved bigger LDL-C level reduction compare to titrating up statin dose [Conard, Scott E., et al 2008] [Leiter, Lawrence A., et al 2008]. The safety of co-administration of ezetimibe and atorvastatin is comparable to ezetimibe or atorvastatin monotherapy. FDC has been shown to be bioequivalent to co-administration of ezetimibe and atorvastatin. Please refer to IB for the details.

2.3 Benefit/Risk Assessment

It cannot be guaranteed that participants in clinical studies will directly benefit from treatment during participation, as clinical studies are designed to provide information about the safety and effectiveness of an investigational medicine.

This is an active control study, and the study interventions have evidenced benefits for study predefined participants regardless of the randomization allocation. In addition, the study procedure, including dose selection and exclusion criteria, was well designed based on robust evidence in terms of safety profile of each component of study interventions from previous studies. And also study will be conducted according to GCP guidelines and highest regulatory requirement in order to ensure the wellbeing of all participants.

Additional details regarding specific benefits and risks for participants participating in this clinical study may be found in the accompanying IB and informed consent documents.

3 HYPOTHESES, OBJECTIVES, AND ENDPOINTS

All objectives and hypotheses will be evaluated in Chinese participants with hypercholesterolemia, inadequately controlled with 10 mg or 20 mg atorvastatin monotherapy.

Objectives	Endpoints
Primary	
• Objective: To evaluate the percent change in LDL-C from baseline to Week 12 of MK-0653C 10/10 mg compared to atorvastatin 20 mg (Cohort A). Hypothesis: MK-0653C 10/10 mg is superior to atorvastatin 20 mg (Cohort A) in percent change from baseline in LDL-C to 12 weeks after treatment. • Objective: To evaluate the percent change in LDL-C from baseline to Week 12 of MK-0653C 10/20 mg compared to atorvastatin 40 mg (Cohort B). Hypothesis: MK-0653C 10/20 mg is superior to atorvastatin 40 mg (Cohort B) in percent change from baseline in LDL-C to 12 weeks after treatment. Overall success is determined by a success on at least one hypothesis.	• Low-Density Lipoprotein – Cholesterol (LDL-C) level

Objectives	Endpoints
Secondary	
• Objective: To evaluate the safety and tolerability of administrated MK-0653C 10/10 mg and MK-0653C 10/20 mg once daily dosing through 12 weeks.	• Adverse events • Laboratory parameters and vital signs • Study drug discontinuation
Exploratory	
• Objective: To evaluate the percentage of participants meeting their LDL-C goals* with administration of MK-0653C 10/10 mg compared to atorvastatin 20 mg (Cohort A), and MK-0653C 10/ 20 mg compared to atorvastatin 40 mg (Cohort B) at Week 12.	• Meeting LDL-C goal (yes, no)
• Objective: To evaluate the percent change in LDL-C from baseline to Week 6 with MK-0653C 10/10 mg compared to atorvastatin 20 mg (Cohort A), and MK-0653C 10/ 20 mg compared to atorvastatin 40 mg (Cohort B).	• LDL-C level
• Objective: To evaluate the percent change in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, triglyceride (TG) and Apoprotein (Apo) B from baseline to Week 6 and Week 12 with MK-0653C 10/10 mg compared to atorvastatin 20 mg (Cohort A), and MK-0653C 10/ 20 mg compared to atorvastatin 40 mg (Cohort B).	• The level of total cholesterol (TC), HDL-C, non- HDL-C, triglyceride (TG) and Apo protein (Apo) B

* The goal attainment values of LDL-C treatments across different ASCVD riskpopulations, detailed information can be found in Table 13 of Appendix 7: 2016 Chinese guidelines for the management of dyslipidemia in adults.

4 STUDY DESIGN

4.1 Overall Design

This is a randomized, active-controlled, parallel-group, multi-site, double-blind study of MK-0653C in Chinese participants with hypercholesterolemia in order to support the marketing authorization in China.

This trial consists of a screening period, an atorvastatin active run-in period, a treatment period and a follow-up period, and the total duration for each participant will be approximately 21 weeks. Participants will enter the run-in period based on their use of statin at the time of screening. After run-in period, 180 participants for Cohort A and 270 participants for Cohort B will be enrolled for randomization.

Participant's eligibility will be assessed based on this risk category and randomization will be stratified according to the risk category as well. Participants diagnosed with elevated LDL-C who are currently treated with low to moderate dose of statins only and not at their target LDL-C goal will be screened up to 2 weeks for the eligibility. Demographic, medical history, lab test review and concomitant medication review or washout if necessary will be conducted. LDL-C treatment goal (Table 13 in Appendix 7) is determined on the basis of the CV risk assessment result (Figure 2) which is evaluated based on the demographic characteristics, medical history and lipid profile according to current Dyslipidemia Management Guidelines in China: 2016 Edition.

People who meet any of the following conditions can be directly listed as a high-risk or very high-risk population

Very high-risk: ASCVD patients

High-risk: (1) LDL-C ≥ 4.9 mmoml/L or TC ≥ 7.2 mmol/L

(2) Diabetes patients [LDL-C: 1.8–4.9 mmol/L (or TC: 3.1–7.2 mmol/L) and age ≥ 40 years]

People who do not meet the conditions, assessment of 10-year incidence risk of ASCVD

*Risk factor	Stratification of serum cholesterol levels (mmol/L)		
	3.1≤ TC ≤ 4.1 or 1.8 ≤ LDL-C < 2.6	4.1 ≤ TC ≤ 5.1 or 2.6 ≤ LDL-C < 3.4	5.2 ≤ TC < 7.2 or 3.4 ≤ LDL-C < 4.9
Without hypertension 0–1	Low-risk (< 5%)	Low-risk (< 5%)	Low-risk (< 5%)
2	Low-risk (< 5%)	Low-risk (< 5%)	Medium-risk (5%–9%)
3	Low-risk (< 5%)	Medium-risk (5%–9%)	Medium-risk (5%–9%)
With hypertension 0	Low-risk (< 5%)	Low-risk (< 5%)	Low-risk (< 5%)
1	Low-risk (< 5%)	Medium-risk	Medium-risk (5%–9%)
2	Medium-risk (5%–9%)	High-risk (≥ 10%)	High-risk (≥ 10%)
3	High-risk (≥ 10%)	High-risk (≥ 10%)	High-risk (≥ 10%)

For people with medium 10-year incidence risk of ASCVD and age < 55 years, assessment of lifetime risk

People with any two or more items of the above risk factors are defined as a high-risk ASCVD population

- Systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg
- Non-HDL-C ≥ 5.2 mmol/L (200 mg/dL)
- HDL-C < 1.0 mmol/L (40 mg/dL)
- BMI ≥ 28 kg/m^2
- Smoking

*Including smoking, low HDL-C, and men ≥ 45 years of age or women ≥ 55 years of age. The risk assessment and treatment of patients with chronic kidney disease refer to the treatment of dyslipidemia in special populations.

ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CM: chylomicron; HDL-C: high-density lipoprotein cholesterol; IDL: intermediate-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; VLDL:very-low-density lipoprotein cholesterol.

Figure 2 The Risk Assessment Flow Chart

(adopted from Dyslipidemia Management Guidelines in China: 2016 Edition, referring to Appendix 7 for more details)

Participants who meet all eligibility criteria will be enrolled in a 5-week active run-in period after they discontinue the current statins with appropriate wash-out interval. Current statin is used to determine the allocation of different cohort: the participants who are currently treated at stable daily dose of 10 mg atorvastatin or other statin equivalent to or less than atorvastatin 10 mg will be assigned to Cohort A and will receive 10 mg atorvastatin during the run-in period; and the participants who are currently treated by atorvastatin at stable 20 mg or other statins equivalent to atorvastatin 20 mg will be assign to cohort B and will receive 20 mg

atorvastatin during the run-in phase. The dose of other statins equivalent to atorvastatin can be found in Table 3.

After the run-in period, the participants within either cohort who have not met their treatment goals for LDL-C according to their risk levels will be randomized into 2 cohorts to receive either MK-0653C or atorvastatin monotherapy (at twice the atorvastatin dose contained in MK-0653C) during a 12 weeks double-blind treatment period:

- Cohort A: Participants will be randomized to receive either MK-0653C 10/10 mg (containing ezetimibe 10 mg + atorvastatin 10 mg) or atorvastatin 20 mg in a 1:1 ratio;

- Cohort B: Participants will be randomized to receive either MK-0653C 10/20 mg (containing ezetimibe 10 mg + atorvastatin 20 mg) or atorvastatin 40 mg in a 1:1 ratio.

Participants who completed the trial or administered at least one dose of study intervention but prematurely discontinued will be followed by phone call 14 days after the last dose to assess serious adverse events (SAEs) and information will be documented on the follow-up visit page.

Specific procedures to be performed during the study, as well as their prescribed times and associated visit windows, are outlined in the SoA in Section 1.3. Details of each procedure are provided in Section 8.

4.2 Scientific Rationale for Study Design

Since the dosage and administration of this FDC is expected to be a second-line therapy in China, MK-0653C will be administered when participants are not well controlled with monotherapy of atorvastatin. The target population of this trial is participants with hypercholesterolemia in whom the lipid management target value of LDL-C as per their CAD-risk category based on Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults has not been achieved, judging from the results of laboratory tests after atorvastatin run-in period and the presence/absence of CAD history.

4.2.1 Rationale for Endpoints

4.2.1.1 Efficacy Endpoints

The primary objective of this trial is to demonstrate superiority of lipid-modifying efficacy of MK-0653C 10/10 mg or 10/20 mg as compared to of atorvastatin monotherapy at twice the atorvastatin dose contained in MK-0653C monotherapy in hypercholesterolemia participants who are not well controlled by the atorvastatin monotherapy. In this trial, the percent change in LDL-C at week 12 from baseline will be used as the primary efficacy endpoint considering the maximum efficacy will be reached at that time point; the percentage of participants achieving their LDL-C goals will be used as the exploratory efficacy endpoint.

LDL-C lowering therapy especially with statin has been proved to be effective for the primary and secondary prevention of Coronary Artery Disease [Stamler, J., et al 1986] [Kannel, W. B., et al 1979] [Castelli, W. P., et al 1983] [Okamura, T., et al 2007]. LDL-C is positioned as a valid biomarker for lipid management, and is used as an important variable for the development of lipid-improving drugs in China, as well as in other countries outside China. In statin studies, the relationship between LDL-C level and the prevention of arteriosclerotic diseases has been well established. The efficacy evaluation based on the percent change in LDL-C as the primary variable has been commonly used in the previous clinical studies of ezetimibe and statins.

4.2.1.2 Safety Endpoints

The safety will be evaluated with clinical and laboratory safety assessments conducted throughout the trial. Centralized liver function test and other biochemistry test will be done at Visit 3, Visit 5 and Visit 6 to detect potential hepatic adverse events and muscle adverse events which were defined as AE of interest. The rational of arrangement is based on the facts as follow. Atorvastatin and Ezetimibe, as the active ingredients, have been authorized and widely used in China as well as worldwide for many years with well-established safety profile. A consistent safety profile is expected of this FDC. According to the label of atorvastatin, the majority of liver function abnormality occurs in first 3 months post the 1st dose, liver function test is suggested to be performed prior to initiation and at 3 month as a standard recommendation according to the label. Atorvastatin, like other statins, occasionally provoke myopathy and rabdomyolysis, especially concomitant use with cyclosporine or potent CYP3A4 inhibitors like clarithorommycin. However, surveillance of creatine kinase (CK) cannot prevent the occurrence of myopathy or rabdomyolysis. Regular surveillance of CK is only recommended when those drugs mentioned above are prescribed for concomitant use as recommended in the label. Ezetimibe was generally well tolerated and when given as concomitant use with statin physicians should refer to the directions for use of statin according to the ezetimibe label. In addition, unnecessary blood test cause participant's burden and can potentially cause the procedure related adverse event, e.g. injection site reaction and negative impact on the willingness of participation.

In addition to the centralized lab test according to the scheduled visits, qualifying local lab can be used to evaluate the eligibility during the screening and also to detect the safety signal during the trial conduction when needed.

Clinical measurements include monitoring of vital signs/physical examination at each visit will be done.Tiered methods will be used for safety endpoints analysis according to severity, frequency and relationship with the drug.

4.2.2 Rationale for the Use of Comparator/Placebo

The Comparator used in this trial is atorvastatin (Lipitor®). Atorvastatin is one of the active components of MK-0653C. In order to demonstrate the additional contribution of the 2nd active component (ezitimibe) in an FDC (MK-0653C), it is commonly required by the agency to demonstrate the superior lipid-modifying efficacy of the FDC compared to

continuing atorvastatin monotherapy (same dose or double dose) in hypercholesterolemia participants who are not well controlled by prior atorvastatin monotherapy. In this trial, atorvastatin 20 mg and 40 mg are being used as the comparators to MK-0653C 10/10 mg and 10/20 mg separately. Please refer to the approved label of Lipitor® for more information about the dose and usage of atorvastatin.

4.3 Justification for Dose

In this trial, MK-0653C 10 (ezetimibe)/10 mg (atorvastatin) and 10 (ezetimibe)/ 20 mg (atorvastatin) were selected. The dosage of ezetimibe is 10 mg once daily. Ezetimibe (EZETROL®) at dose of 10 mg has been approved in China since 2006; it is the only approved dose in China and has an abundance of clinical use experience both as monotherapy and combination therapy in Asian patients.

The brand atorvastatin product, Lipitor® tablets, has been marketed since 1999 in China. The usual clinical dosage of atorvastatin is 10 mg once daily and may be increased up to 40 mg for patients with hypercholesterolemia. Post-marketing survey of atorvastatin showed that Lipitor® at 10 mg or 20 mg are often be co-administered with brand ezetimibe, EZETROL® 10 mg [Teramoto, T., et al 2012].

In consideration of the efficacy and safety profiles of atorvastatin, and clinical position of MK-0653C, we have found that 10 or 20 mg is an appropriate dose to be combined for atorvastatin.

4.4 Beginning and End of Study Definition

The overall study begins when the first participant signs the ICF. The overall study ends when the last participant completes the last study-related telephone-call or visit, withdraws from the study, or is lost to follow-up (ie, the participant is unable to be contacted by the investigator).

4.4.1 Clinical Criteria for Early Study Termination

The clinical study may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the study population as a whole is unacceptable. In addition, further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, Good Clinical Practice (GCP), and/or other applicable regulatory requirements, procedure-related problems or an unacceptably high number of discontinuations or withdrawals due to administrative reasons.

5 STUDY POPULATION

Male/Female participants between the ages of 18 and 80 years (inclusive) with hypercholesterolemia and inadequately controlled by low to median dose of statins only (see below) will be enrolled in this study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 Inclusion Criteria

To be eligible for inclusion in this study, the participant must:

Visit 1 and 2 Criteria

Participants should meet these criteria at Visit 1 and Visit 2.

1. Participant with hypercholesterolemia diagnosed by investigator according to Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (2016 Edition).

2. Participant has been stabilized on atorvastatin treatment at 10 mg (other statins with LDL-C lowering efficacy equivalent to or less than atorvastatin 10 mg) or 20 mg (or other statins with LDL-C lowering efficacy equivalent to 20 mg, refer to Table 3) for at least 4 weeks prior to Visit 1.

Demographics

3. Participant is male or female.

4. Participant is from 18 years to 80 years of age inclusive, at the time of signing the informed consent.

5. Male Participants

Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A male participant must agree to use contraception as detailed in Appendix 5 of this protocol from the time of providing informed consent through completion of the study and refrain from donating sperm during this period.

6. Female Participants

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 from the time of providing informed consent through completion of the study.

Informed Consent

7. Participant (or legally acceptable representative if applicable) provides written informed consent/assent for the study.

Additional Categories

8. Participant agree to maintained a stable diet and stable exercise during the study.

Visit 4 Criteria

9. Participant has completed the 5-week atorvastatin run-in period.

10. Participant has ≥75% compliance with study medication during the atorvastatin run-in period.

11. Participant meets any of the following criteria on LDL-C level based on the lipid panel test at Visit 3.

    a. For medium or low risk participants: ≥130 mg/dL (3.4 mmol/L).

    b. For high risk participants: ≥100 mg/dL (2.6 mmol/L) and ≤160 mg/dL (4.1 mmol/L).

    c. For very high risk participants: ≥70 mg/dL (1.8 mmol/L) and ≤160 mg/dL (4.1 mmol/L).

5.2 Exclusion Criteria

The participant must be excluded from the study if the participant:

Visit 1 Criteria

Medical Conditions

1. Participant had a uncontrolled hypertriglyceridemia which needs drug intervention or a fasting triglyceride (TG) value ≥ 500 mg/dL (4.52 mmol/L) at Visit 1.

2. Participant is currently treated with statin at dose of equivalent LDL-C lowering effect greater than 20 mg atorvastatin.

3. Participants has active liver disease at Visit 1 or lab test evidenced liver transaminases (ALT and AST) > 2 X upper limit of normal (ULN) per central laboratory at Visit 1 or local lab within 4 weeks prior to the screening visit.

4. Participant has NYHA (New York Heart Association) Class III or IV symptomatic congestive heart failure at Visit 1.

5. Participant has uncontrolled cardiac arrhythmias, myocardial infarction (MI), PCI, CABG, unstable angina, or stroke within 3 months (12 weeks) prior to Visit 1.

6. Participant has homozygous familial hypercholesterolemia or has undergone LDL apheresis.

7. Participant has endocrine or metabolic disease known to influence serum lipids or lipoproteins (i.e., secondary causes of hyperlipidemia, e.g., hyper or hypothyroidism, Cushing's syndrome) at Visit 1.

8. Participant has an estimated glomerular filtration rate (eGFR) < 30 mL/min /1.73m^2 or other clinical significant renal disease which needs intensive medical care (e.g. systematic use of steroids/immunosuppressant, renal transplant, hemodialysis, etc.) at Visit 1. eGFR calculation is based on the below equation:

   Male: eGFR [mL/min/1.73m^2] =194 x Cr [mg/dL] -1.094 x age [yr] -0.287

   Female: eGFR[mL/min/1.73m^2]=194 x Cr [mg/dL] -1.094 x age [yr] -0.287 x 0.739

9. Participant has had a gastrointestinal tract bypass, or other significant intestinal malabsorption.

10. Participant has a history of cancer within the past 5 years from Visit 1 (except for successfully treated dermatological basal cell or squamous cell carcinoma or in situ cervical cancer).

11. Participant who is known human immunodeficiency virus (HIV) positive (as assessed by medical history).

12. Participant has hypersensitivity or intolerance to ezetimibe, atorvastatin, the ezetimibe/atorvastatin combination tablet, or any component of these medications or has a condition or situation, which described as contraindication in labeling of EZETROL® or Lipitor® or may interfere with participation in the trial in the opinion of the investigator.

13. Participant has disorders of the hematologic, digestive, or central nervous systems including cerebrovascular disease and degenerative disease that in the opinion of the investigator would limit evaluation or participation.

14. Participant has a history of mental instability, drug/alcohol abuse within the past 5 years, or major psychiatric illness not adequately controlled and stable on pharmacotherapy in the investigator's judgement.

15. Participant has a history of myopathy or rhabdomyolysis with ezetimibe or any statin.

16. Participant has a medical condition or personal circumstance which, in the opinion of the investigator, places the participant at unnecessary risk through continued participation in the trial or does not allow the participant to adhere to the requirements of the protocol.

17. A WOCBP who has a positive urine pregnancy test within 24 hours before the first dose of study intervention. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Prior/Concomitant Therapy

18. Participant is currently taking medications that are potent modulators of cytochrome P-450 3A4 (CYP3A4) including:

    - Cyclosporine
    - Systemically administered azole antifungals such as ketoconazole, fluconazole, and itraconazole
    - Macrolide antibiotics (e.g., clarithromycin, and erythromycin)
    - Protease inhibitors (e.g., ritonavir, saquinavir, and lopinavir)
    - Grapefruit or juice of grapefruit (200 ml/day for more than 3 times per week).

19. Participant is taking any cyclical hormones (e.g., cyclical oral contraceptives, cyclical hormone replacement), including the combination of ethinyl estradiol and norethisterone, or non-cyclical hormones, including non-cyclical hormone replacement therapy (HRT) or any estrogen antagonist/agonist within 8 weeks.

    Note: If participant has been treated with a stable regimen of non-cyclical HRT for > 8 weeks and agree to continue this regimen for the duration of the trial, concomitant therapy is acceptable.

20. Participant is receiving treatment with systemic corticosteroids (intravenous, intramuscular and oral steroids).

21. Participant is treated with psyllium, other fiber-based laxatives, phytosterol margarine, and herbal medicine and/or over the counter (OTC) therapies that are known to affect serum lipids.

    Note: If participant has been treated with a stable regimen for > 8 weeks and agree to continue this regimen for the duration of the trial, concomitant therapy is acceptable.

22. Participant is treated with an anti-obesity drug (e.g. mazindol) within 12 weeks prior to Visit 1.

23. Participant is treated with warfarin or warfarin-like anticoagulants and has not been on a stable dose with a stable International Normalized Ratio (INR) for at least 6 weeks.

24. Participant has taken lipid-lowering agents (except probucol) including, Cholestin™, bile acid sequestrants, ezetimibe, fibrates or niacin (>200 mg/day), PCSK9 inhibitors within 6 weeks prior to Visit 1. Participant has taken probucol within 10 weeks prior to Visit 1.

Prior/Concurrent Clinical Study Experience

25. Participant who has been treated with any other investigational drug within 30 days of Visit 1.

Diagnostic Assessments

Not applicable.

Other Exclusions

26. Participant who currently follows an excessive weight reduction diet in the opinion of the investigator.

27. Participant currently engages in a vigorous exercise regimen (e.g.; marathon training, body building training) or intends to starts training during the trial.

28. Is or has an immediate family member (eg, spouse, parent/legal guardian, sibling, or child) who is investigational site or Sponsor staff directly involved with this study.

Visit 4 Criteria

29. Participant reaches the treatment goal with mono-statin therapy [per central lab].

30. Participant has creatine kinase (CK) levels > 3 X ULN [per central laboratory reference ranges].

31. Participant has developed a new medical condition, suffered a change in status of an established medical condition or required a new treatment or medication, which meets any, previously described trial exclusion criteria.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Participants should be instructed for diet or a similar diet according to China 2016 Guideline at Visit 1. Participants also should keep exclusion criteria 24 (Participant consumes less than 0.2 L of grape fruit juice per day.) during trial period.

At each subsequent trial visit, the dietary compliance will be monitored and sites should reinstruct participants who are not compliant. This monitoring is particularly important in an effort to minimize any diet-related lipid changes.

Participants should fast (no food or drink except water) for at least 10 hours prior to all scheduled trial visits. Permitted concomitant therapies can be taken during the fasting period.

Note: If the participant reports to the visit without having fasted, the sample should not be drawn, and the participant should be asked to return for another appointment.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

Participants will be suggested not consume more than the 25 g alcohol per day.

Participants will not be permitted in the trial if they consistently consume excessive amounts of alcohol. Participants should be encouraged not to make major changes in their alcohol consumption for the duration of the trial. Please refer to Table 1 for reference volume of alcohol.

Table 1 Alcohol Consumption Quantities

Alcohol	25 g/day
Beer	1 bottle (633 ml/bottle)
Sake	180 ml
Whiskey/ Brandy	2.5 glasses (single)
Distilled spirit	90 ml
Wine	2 glasses

Participants should refrain from smoking during the trial.

5.3.3 Activity Restrictions

Participants should continue any activity he/she was accustomed to prior to entering the trial, but should refrain from engaging in a vigorous exercise regimen during the trial. Participants should be instructed the activity by investigator based on Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults. Participant also should keep Exclusion Criterion 27 and 28 (Participant does not follow excessive weight reduction diet from trial duration, and does not engage in a vigorous exercise regimen or start training) during the trial.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently enter the run-in epoch in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography,

screen failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements as outlined in the data entry guidelines.

5.5 Run-in Failure

For participants successfully screened but discontinued during the treatment run-in period must be carefully documented with the reason in the appropriate CRF, and these participants are considered treatment run-in failures.

No re-screening of participants that are discontinued from the run-in period will be allowed.

5.6 Participant Replacement Strategy

A participant who discontinues from study intervention will not be replaced.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

Clinical supplies [study intervention(s) provided by the Sponsor] will be packaged to support enrollment . Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

6.1 Study Intervention(s) Administered

The study intervention(s) to be used in this study are outlined in Table 2.

Each assigned study interventions will be administered orally once daily. As there is no recommended dosing time, the participant should take their treatment at a consistent time each day and participants are suggested to avoid taking the study intervention with other concomitant medications at the same time. On the visit day, the participant should take the medication after all procedures are completed.

Table 2 Study Interventions

During active run-in period:

Cohort Name	Cohort Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP/NIMP	Sourcing
A	Active Comparator	atorvastatin	Drug	Tablet	10 mg	10 mg QD	Oral	Run-in period/ 5 weeks	Active treatment to select uncontrolled participants	NIMP	Provided centrally by the Sponsor
B	Active Comparator	atorvastatin	Drug	Tablet	20 mg	20 mg QD	Oral	Run-in period/ 5 weeks	Active treatment to select uncontrolled participants	NIMP	Provided centrally by the Sponsor
Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.											

During double-blinded treatment period:

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
A1	Experi-mental	MK-0653C FDC (ezetimibe 10 mg + atorvastatin 10 mg)	Drug	Tablet	10 mg / 10 mg	10 mg / 10 mg QD	Oral	Randomization treatment: 12 weeks	Experimental	IMP	Provided centrally by the Sponsor
	Placebo	Placebo atorvastatin	Drug	Tablet	0 mg	0 mg QD	Oral	Randomization treatment: 12 weeks	Dummy with study treatment	NIMP	Provided centrally by the Sponsor
A2	Active Comparator	atorvastatin	Drug	Tablet	20 mg	20 mg QD	Oral	Randomization treatment: 12 weeks	Active control	NIMP	Provided centrally by the Sponsor
	Placebo	Placebo of MK-0653C FDC (ezetimibe 10 mg + atorvastatin 10 mg)	Drug	Tablet	0 mg	0 mg QD	Oral	Randomization treatment: 12 weeks	Dummy with study treatment	NIMP	Provided centrally by the Sponsor
B1	Experi-mental	MK-0653C FDC (ezetimibe 10 mg + atorvastatin 20 mg)	Drug	Tablet	10 mg / 20 mg	10 mg / 20 mg QD	Oral	Randomization treatment: 12 weeks	Experimental	IMP	Provided centrally by the Sponsor
	Placebo	Placebo of atorvastatin	Drug	Tablet	0 mg	0 mg QD	Oral	Randomization treatment: 12 weeks	Dummy with study treatment	NIMP	Provided centrally by the Sponsor

Arm Name	Arm Type	Intervention Name	Type	Dose Formulation	Unit Dose Strength(s)	Dosage Level(s)	Route of Adminis-tration	Regimen/ Treatment Period	Use	IMP/ NIMP	Sourcing
B2	Active Comparator	atorvastatin	Drug	Tablet	20 mg	40 mg QD	Oral	Randomization treatment: 12 weeks	Active control	NIMP	Provided centrally by the Sponsor
	Placebo	Placebo of MK-0653C FDC (ezetimibe 10 mg+atorvastatin 20 mg)	Drug	Tablet	0 mg	0 mg QD	Oral	Randomization treatment: 12 weeks	Dummy with study treatment	NIMP	Provided centrally by the Sponsor
Definition Investigational Medicinal Product (IMP) and Non-Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed. The first dose of trial treatment will be administered at the trial site at Visit 4. Subsequent dosing will be performed once daily by the participant (i.e., unsupervised at his/her home) at approximately the same time each day.											

All supplies indicated in Table 2 will be provided per the "Sourcing" column depending upon local country operational requirements. If local sourcing, every attempt should be made to source these supplies from a single lot/batch number where possible (e.g., not applicable in the case where multiple lots or batches may be required due to the length of the study, etc).

Refer to Section 8.1.8 for details regarding administration of the study intervention.

All placebos were created by the Sponsor to match the active product.

6.2 Preparation/Handling/Storage/Accountability

6.2.1 Dose Preparation

There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each participant. The rationale for selection of doses to be used in this study is provided in Section 4.3.

6.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.3 Measures to Minimize Bias: Randomization and Blinding

6.3.1 Intervention Assignment

Intervention allocation/randomization will occur centrally using an interactive response technology (IRT) system. There are 2 cohorts with 2 study intervention arms in each cohort. Algorithm of participant's allocation is based on current statin dose prior to the screening (a stable dose is required at least 4 weeks prior to Visit 1). For participants who is currently treated with atorvastatin 10 mg or equivalent or equivalents less than 10 mg atorvastatin will be assigned to cohort A; while other participants who is currently under treatment of 20 mg atorvastatin or equivalents will be assigned to cohort B (atorvastatin and other equivalent statin can be found in Table 3). Within each cohort, participants will be assigned randomly in a 1:1 ratio to receive MK-0653C or atorvastatin treatment, respectively.

Table 3 Dose of Atorvastatin and Other Equivalent Statin

Cohort	Atorvastatin (mg)	Simvastatin (mg)	Lovastatin (mg)	Pravastatin (mg)	Fluvastatin (mg)
A	-	10	20	20	40
A	10	20	40	40	80
B	20	40	80	-	-

6.3.2 Stratification

Intervention allocation/randomization will be stratified according to the following factors:

- Cohort (i.e., Cohort A – atorvastatin ≤10 mg or equivalent and Cohort B – atorvastatin 20 mg or equivalent).
- Disease risk category (low, moderate, high, and very high risk, referred to Section 4.1).

6.3.3 Blinding

A double-blinding technique with in-house blinding will be used. A double-dummy design is used because the identity of MK-0653C and comparator (atorvastatin) cannot be disguised due to different appearance. The participant, the investigator, and Sponsor personnel or delegate(s) who are involved in the study intervention administration or clinical evaluation of the participants are unaware of the intervention assignments.

6.4 Study Intervention Compliance

Interruptions from the protocol-specified treatment plan needs to be documented, for those interruption >=25% from the treatment plan will require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

6.5 Concomitant Therapy

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medications or vaccinations specifically prohibited, discontinuation from study intervention may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the participant's primary physician. However, the decision to continue the participant on study intervention requires the mutual agreement of the investigator, the Sponsor, and the participant.

Specific restrictions are listed in Table 4 for concomitant therapy or vaccination:

Table 4 Prohibited Medications

Exclu-sion	Class	Details	Prohibi-tion Start	Note
18	CYP3A4 modulators	Cyclosporine; Systemically administered azole antifungals such as ketoconazole, fluconazole, and itraconazole; Macrolide antibiotics (e.g., clarithromycin, erythromycin); Protease inhibitors (e.g., ritonavir, saquinavir, lopinavir); Grapefruit or juice of grapefruit (the amount should not be over 200 ml/day, and should not be consumed 3 consecutive days or longer).	V1	
19	Cyclical hormones and Non-cyclical hormones	Cyclical hormones (cyclical oral contraceptives, cyclical hormone replacement) including the combination of ethinyl estradiol, norehisterone; Non-cyclical hormone therapy (including non-cyclical hormone replacement therapy or any estrogen antagonist/agonist).	V1	If the participant takes cyclical hormones (e.g., cyclical oral contraceptives, cyclical hormone replacement), including the combination of ethinyl estradiol and norethisterone, or non-cyclical hormones, including non-cyclical hormone replacement therapy or any estrogen antagonist/agonist, these treatment should be stably taken more than 8 weeks and supposed to be taken at the same dosage
20	Corticosteroids	Systemic corticosteroids (intravenous, intramuscular and oral steroids)	V1	Topical, intra-articular, nasal, inhaled and ophthalmic steroid therapies are allowed.
21	Agents potentially affect serum lipids	psyllium, other fiber-based laxatives, phytosterol margarine, herbal medicine and/or over the counter (OTC) therapies	8 weeks prior to V1	If the participant has been treated with a stable regimen for > 8 weeks prior to Visit 1 and agree to continue this regimen for the duration of the trial, concomitant therapy is acceptable.

Exclu-sion	Class	Details	Prohibi-tion Start	Note
22	Anti-obesity drug	Mazindol	12 weeks prior to V1	
23	warfarin	Warfarin or warfarin-like anticoagulants and has not been on a stable dose with a stable INR.	V1	Warfarin or warfarin-like anticoagulants therapy is acceptable, if the participant must be on a stable dose with a stable INR for 6 weeks prior to Visit 1.
24	Lipid lowering agents	Cholestin TM, bile acid sequestrants, Ezetimibe, fibrates or niacin (>200 mg/day)	6 weeks prior to V1	
		Probucol	10 weeks prior to V1	
		Statin other than atorvastatin, Ezetimibe other than the ezetimibe component of MK-0653C	V1	

6.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified for use in this study.

6.6 Dose Modification (Escalation/Titration/Other)

No dose modifications are planned for this study.

6.7 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

6.8 Clinical Supplies Disclosure

The emergency unblinding call center will use the intervention/randomization schedule for the study to unblind participants and to unmask study intervention identity . The emergency unblinding call center should only be used in cases of emergency (see Section 8.1.1 1). In the event that the emergency unblinding call center is not available for a given site in this study, the central electronic intervention allocation/randomization system (IRT) should be used to unblind participants and to unmask study intervention identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

Each study site will be supplied by Sponsor with the investigational treatment.

6.9 Standard Policies

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IRT system) to allocate participants, to assign treatment to participants and to manage the distribution of clinical supplies. Each person accessing the IRT system must be assigned an individual unique participant identification number (PIN). They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT WITHDRAWAL

7.1 Discontinuation of Study Intervention

Discontinuation of study intervention does not represent withdrawal from the study.

As certain data on clinical events beyond study intervention discontinuation may be important to the study, they must be collected through the participant's last scheduled follow-up, even if the participant has discontinued study intervention. Therefore, all participants who discontinue study intervention prior to completion of the protocol-specified treatment period will still continue to participate in the study as specified in Section 1.3 and Section 8.11.4.

Participants may discontinue study intervention at any time for any reason or be discontinued from the study intervention at the discretion of the investigator should any untoward effect occur. In addition, a participant may be discontinued from study intervention by the investigator or the Sponsor if study intervention is inappropriate, the study plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at study intervention discontinuation are provided in Section 8.1.10.

A participant must be discontinued from study intervention but continue to be monitored in the study for any of the following reasons:

- The participant or participant's legally acceptable representative requests to discontinue study intervention.
- The participant has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, placed the participant at unnecessary risk from continued administration of study intervention.
- The participant has a confirmed positive serum pregnancy test.
- Consecutive (2 or more measurements within 1 week) elevations in ALT or AST ≥3 x ULN.

- Consecutive(2 or more measurements within 1 week) elevations in CK ≥10 x ULN with or without muscle symptoms.

- Consecutive (2 or more measurements within 1 week) elevations in CK ≥5 to <10 x ULN with muscle symptoms.

- The participant is requiring any treatment with telaprevir or fibrates.

- The participants are requiring any treatment with a potent inhibitor of cytochrome P450 3A4 (CYP3A4) such as, itraconazole, ketoconazole, erythromycin, clarithromycin or HIV protease inhibitors for their emerging medical conditions.

- Moved (or relocated): When the participant has either moved or relocated and is no longer able to participate in the trial.

- Participant developed a new condition which needs more intensive statin treatment or LDL-C lowing treatment.

For participants who are discontinued from study intervention but continue to be monitored in the study, all visits and procedures, as outlined in the SoA, should be completed.

7.2 Participant Withdrawal From the Study

A participant must be withdrawn from the study if the participant or participant's legally acceptable representative withdraws consent from the study.

If a participant withdraws from the study, they will no longer receive study intervention or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the study, are outlined in Section 8.1.10. The procedures to be performed should a participant repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the participant are outlined in Section 7.3.

7.3 Lost to Follow-up

If a participant fails to return to the clinic for a required study visit and/or if the site is unable to contact the participant, the following procedures are to be performed:

- The site must attempt to contact the participant and reschedule the missed visit. If the participant is contacted, the participant should be counseled on the importance of maintaining the protocol-specified visit schedule.

- The investigator or designee must make every effort to regain contact with the participant at each missed visit (eg, telephone calls and/or a certified letter to the participant's last known mailing address or locally equivalent methods). These contact attempts should be documented in the participant's medical record.

- Note: A participant is not considered lost to follow-up until the last scheduled visit for the individual participant. The missing data for the participant will be managed via the prespecified statistical data handling and analysis guidelines.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA.

- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

- The investigator is responsible for ensuring that procedures are conducted by appropriately qualified or trained staff. Delegation of study site personnel responsibilities will be documented in the Investigator Trial File Binder (or equivalent).

- All study-related medical decisions must be made by an investigator who is a qualified physician.

- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and were performed within the time frame defined in the SoA.

- Additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to participant safety. In some cases, such evaluation/testing may be potentially sensitive in nature (eg, HIV, Hepatitis C), and thus local regulations may require that additional informed consent be obtained from the participant. In these cases, such evaluations/testing will be performed in accordance with those regulations.

The sample collection from each participant over the study is served to prove the efficacy and safety of the study intervention and will be described in laboratory manual.

Local laboratory use is allowed for the purpose of close monitoring of safety signals and should follow the site's clinical practice.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Administrative and General Procedures

8.1.1 Informed Consent

The investigator or medically qualified designee (consistent with local requirements) must obtain documented consent from each potential participant or each participant's legally acceptable representative prior to participating in a clinical study. If there are changes to the participant's status during the study (eg, health or age of majority requirements), the investigator or medically qualified designee must ensure the appropriate consent is in place.

8.1.1.1 General Informed Consent

Consent must be documented by the participant's dated signature or by the participant's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the participant before participation in the study.

The initial ICF, any subsequent revised written ICF, and any written information provided to the participant must receive the Institutional Review Board/Independent Ethics Committee's (IRB/IEC's) approval/favorable opinion in advance of use. The participant or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the participant's dated signature or by the participant's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/IEC requirements, applicable laws and regulations, and Sponsor requirements.

8.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator who is a qualified physician to ensure that the participant qualifies for the study.

8.1.3 Participant Identification Card

All participants will be given a participant identification card identifying them as participants in a research study. The card will contain study site contact information (including direct telephone numbers) to be used in the event of an emergency. The investigator or qualified designee will provide the participant with a participant identification card immediately after

the participant provides written informed consent. At the time of intervention allocation/randomization, site personnel will add the treatment/randomization number to the participant identification card.

The participant identification card also contains contact information for the emergency unblinding call center so that a healthcare provider can obtain information about study intervention in emergency situations where the investigator is not available.

8.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.

8.1.5 Prior and Concomitant Medications Review

8.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the participant within 12 weeks before the Visit 1. Please note that the prior medications for the treatment of hypercholesterolemia must be documented in eCRF.

8.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the participant during the study.

8.1.6 Assignment of Screening Number

All consented participants will be given a unique screening number that will be used to identify the participant for all procedures that occur prior to randomization. Each participant will be assigned only 1 screening number. Screening numbers must not be re-used for different participants.

8.1.7 Assignment of Treatment/Randomization Number

All eligible participants will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the participant for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization number is assigned to a participant, it can never be re-assigned to another participant.

A single participant cannot be assigned more than 1 treatment/randomization number.

Randomization number will be allocated at Week 0 (Visit 4) via IVRS/IWRS.

8.1.8 Study Intervention Administration

Administration of first study dosing during randomization phase will be witnessed by the investigator and/or study staff at study site. Subsequent dosing will be performed once daily by the participant (i.e., unsupervised at his/her home).Since MK-0653C and atorvastatin differ in appearance thus corresponding matching placebos will be provided to ensure the efficient blinding. Participants who successfully pass the eligibility check at Visit 4 will be randomized within each cohort and will receive one bottle (20 mg atorvastatin or matching placebo) and one blister (MK-0653C or matching placebo) of study treatments during the double-blinded treatment period. Participants should be instructed to take 1 (for Cohort A) or 2 (for Cohort B) tablets from bottle and 1 tablet from blister every day during the study (i.e., Cohort A: either 1 tablet of MK-0653C 10/10 mg and 1 tablet of placebo matched to 20 mg atorvastatin OR 1 tablet of atorvastatin 20 mg and 1 tablet of placebo matched to 10/10 mg MK-0653C; Cohort B: either 1 tablet of MK-0653C 10/20 mg and 2 tablets of placebo matched to 20 mg atorvastatin OR 2 tablets of atorvastatin 20 mg and 1 tablet of placebo matched to 10/20 mg MK-0653C).

Participants will be provided with enough study treatment to last between study site visits.

8.1.8.1 Timing of Dose Administration

Administration of study medication will be performed once daily at approximately the same time each day for 12 weeks during the double-blinded treatment period, without regard to the time of meals.

8.1.9 Trial Compliance (Medication/Diet/Activity/Other)

Adherence to study treatment will be assessed by tablet countat Visit 4-6. Participants with ≥75% compliance during run-in period will be eligible for study entry.

Every effort must be made to maintain adherence to study treatment dosing per protocol as close to 100% as possible. Interruptions from the protocol specified treatment plan for compliance<75% require consultation between investigator and Sponsor.

Paicipant will be instructed for prohibited medication according to the protocol exclusion criteria. And also participant will be instructed for diet, or a similar diet and life style according to China 2016 Guideline at Visit 1. Investigator will check any changes at each visit regarding concomitant medication, diet and life style, and document the changes on eCRF dedicated page.

8.1.10 Discontinuation and Withdrawal

Participants who discontinue study intervention prior to completion of the predefined treatment period for any reason at any time can restart the study intervention. However, participants are expected to rechallenge the study intervention at the earliest time upon decision of the investigator, and all premature discontinued participants should be encouraged to continue to be followed for all remaining study visits , regardless of the rechallenge, as outlined in the SoA and Section 8.11.3.

When a participant withdraws from participation in the study, all applicable activities scheduled for the end of study visit should be performed (at the time of withdrawal). Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements outlined in Section 8.4 and 8.11.

8.1.11 Participant Blinding/Unblinding

STUDY INTERVENTION IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or medically qualified designee (consistent with local requirements) needs to identify the intervention used by a participant and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or medically qualified designee, the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the Sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a participant's intervention assignment, the investigator who is a qualified physician should make reasonable attempts to enter the intensity of the AEs observed, the relation to study intervention, the reason thereof, etc., in the medical chart. If it is not possible to record this assessment in the chart prior to the unblinding, the unblinding should not be delayed.

In the event that unblinding has occurred, the circumstances around the unblinding (eg, date, reason, and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible.Once an emergency unblinding that is part of the study design has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the participant.

Participants will remain blind to the identity of the treatment from Visit 4 until database lock, using the following methods:

- Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone involved in the study;
- The identity of the treatment will be concealed by using the identical packaging, labeling, appearance, taste and color. And a double-dummy design is used because differences between investigational treatment and comparator cannot be disguised due to their different appearance;
- Lipid panel test after randomization will be done centrally and the result will not reveal to the participants or study team until end of the study. No attempts could be made to have local evaluation of the lipid levels once the participant successfully entered the double blind treatment phase.

8.1.12 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical study that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the study site.

8.2 Efficacy Assessments

8.2.1 Clinical Efficacy Laboratory Assessments

Fasting blood samples (obtained at least 10 hours after intake of last meal/food/beverage other than water) will be drawn as outlined in the SoA. The central laboratory will perform all laboratory test determinations from Visit 3 till Visit 6 (Appendix 2). LDL-C will be calculated using the Friedewald method when TG ≤400 mg/dL and beta quantification ultracentrifugation when TG>400 mg/dL. All Lipid Panel A and Apo B data will be blinded once the participant is centrally randomized. Once a participant is randomized (Visit 4), no attempts should be made on the part of the investigator or participant to have a local evaluation of the participant's lipid values (Lipid Panel A and Apo B).

8.3 Safety Assessments

The assessment of safety will be based primarily on the frequency of AEs, SAEs, and laboratory abnormalities. Other safety data will be summarized as appropriate.

1. Laboratory evaluations (performed at baseline and at the end of the study)

2. Adverse events and serious adverse events, adverse events of interest including muscular event and hepatic events (performed throughout full study)

3. Discontinuation due to AEs (performed throughout full study)

4. Physical Exam (performed throughout full study)

5. Vital signs (performed throughout full study)

Details regarding specific safety procedures/assessments to be performed in this study are provided. The total amount of blood/tissue to be drawn/collected over the course of the study (from prestudy to poststudy visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per participant, can be found in Section 8.

Planned time points for all safety assessments are provided in the SoA.

8.3.1 Physical Examinations

A complete physical examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) as per institutional standard at screening and scheduled timepoint.

Height and weight will also be measured and recorded. Body height and weight will be obtained with the participants shoes off, jacket or coat removed, using a standardized scale.

The investigator will determine if the results are clinically significant prior to Week 0 (Visit 4), any physical examination abnormalities will be recorded as part of the participant's medical history. Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2 Vital Signs

- Heart rate and blood pressure will be assessed.

- Blood pressure and pulse measurements will be assessed in sitting position with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions.

- Vital signs (to be taken before blood collection for laboratory tests, or at least 5 minutes afterwards) will consist of 1 pulse and 3 blood pressure measurements (after the participant has been sitting for 5 minutes, 3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute).

- Any clinically significant change from baseline for vital sign measurement (not associated with another adverse event) will be recorded.

8.3.3 Electrocardiograms

- 12-lead electrocardiogram (ECG) will be obtained and reviewed by an investigator or medically qualified designee (consistent with local requirements) as outlined in the SoA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

- The investigator will determine if the results are clinically significant and they meet the eligibility criteria. Any ECG abnormalities at screening visit will be recorded as part of the participant's medical history.

8.3.4 Clinical Safety Laboratory Assessments

Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.

- The investigator or medically qualified designee (consistent with local requirements) must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the case report form (CRF). The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.

- If laboratory values from nonprotocol specified laboratory assessments performed at the institution’s local laboratory require a change in study participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the appropriate CRF (eg, SLAB).

- For any laboratory tests with values considered clinically significantly abnormal during participation in the study or within 14 days after the last dose of study intervention, every attempt should be made to perform repeat assessments until the values return to normal or baseline or if a new baseline is established as determined by the investigator.

8.4 Adverse Events (AEs), Serious Adverse Events (SAEs), and Other Reportable Safety Events

The definitions of an AE or SAE, as well as the method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting AE, SAE, and other reportable safety event reports can be found in Appendix 3.

Adverse events, SAEs, and other reportable safety events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for following up AEs, SAEs, and other reportable safety events for outcome according to Section 8.4.3.

The investigator, who is a qualified physician, will assess events that meet the definition of an AE or SAE as well as other reportable safety events with respect to seriousness, intensity/toxicity and causality.

8.4.1 Time Period and Frequency for Collecting AE, SAE, and Other Reportable Safety Event Information

All AEs, SAEs, and other reportable safety events that occur after the consent form is signed but before intervention allocation/randomization must be reported by the investigator if the participant is receiving placebo run-in or other run-in treatment, if the event causes the participant to be excluded from the study, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, or a procedure.

From the time of intervention allocation/randomization through 14 days following cessation of treatment, all AEs, SAEs, and other reportable safety events must be reported by the investigator.

Additionally, any SAE brought to the attention of an investigator at any time outside of the time period specified in the previous paragraph must be reported immediately to the Sponsor if the event is considered related to study intervention.

Investigators are not obligated to actively seek AEs or SAEs or other reportable safety events in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor.

All initial and follow-up AEs, SAEs, and other reportable safety events will be recorded and reported to the Sponsor or designee within the time frames as indicated in Table 5.

Table 5 Reporting Time Periods and Time Frames for Adverse Events and Other Reportable Safety Events

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Nonserious Adverse Event (NSAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Not required	Per data entry guidelines

Type of Event	**Reporting Time Period: Consent to Randomization/ Allocation**	**Reporting Time Period: Randomization/ Allocation through Protocol-specified Follow-up Period**	**Reporting Time Period: After the Protocol-specified Follow-up Period**	**Time Frame to Report Event and Follow-up Information to Sponsor:**
Serious Adverse Event (SAE)	Report if: - due to protocol-specified intervention - causes exclusion - participant is receiving placebo run-in or other run-in treatment	Report all	Report if: - drug/vaccine related. (Follow ongoing to outcome)	Within 24 hours of learning of event
Pregnancy/Lactation Exposure	Report if: - due to intervention - causes exclusion	Report all	Previously reported – Follow to completion/termination; report outcome	Within 24 hours of learning of event
Event of Clinical Interest (require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - Potential drug-induced liver injury (DILI) - Require regulatory reporting	Not required	Within 24 hours of learning of event
Event of Clinical Interest (do not require regulatory reporting)	Report if: - due to intervention - causes exclusion	Report - non-DILI ECIs and those not requiring regulatory reporting	Not required	Within 5 calendar days of learning of event
Cancer	Report if: - due to intervention - causes exclusion	Report all	Not required	Within 5 calendar days of learning of event
Overdose	Report if: - receiving placebo run-in or other run-in medication	Report all	Not required	Within 5 calendar days of learning of event

8.4.2 Method of Detecting AEs, SAEs, and Other Reportable Safety Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs and other reportable safety events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.4.3 Follow-up of AE, SAE, and Other Reportable Safety Event Information

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs, SAEs, and other reportable safety events including pregnancy and exposure during breastfeeding, events of clinical interest (ECIs), cancer, and overdose will be followed until resolution, stabilization, until the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). In addition, the investigator will make every attempt to follow all nonserious AEs that occur in randomized participants for outcome. Further information on follow-up procedures is given in Appendix 3.

8.4.4 Regulatory Reporting Requirements for SAE

Prompt notification (within 24 hours) by the investigator to the Sponsor of SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply wth country-specific regulatory requirements and global laws and regulations relating to safety reporting to regulatory authorities, IRB/IECs, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAE) from the Sponsor will file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.5 Pregnancy and Exposure During Breastfeeding

Although pregnancy and infant exposure during breastfeeding are not considered AEs, any pregnancy or infant exposure during breastfeeding in a participant (spontaneously reported to the investigator or their designee) that occurs during the study are reportable to the Sponsor.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

8.4.6 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Refer to Appendix 3.

8.4.7 Events of Clinical Interest (ECIs)

Selected nonserious and SAEs are also known as ECIs and must be reported to the Sponsor.

Events of clinical interest for this study include:

1. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The study site guidance for assessment and follow-up of these criteria can be found in the Investigator Study File Binder (or equivalent).

2. An overdose of Sponsor's product, as defined in Section 8.5, that is not associated with clinical symptoms or abnormal laboratory results.

3. Myopathy, rhabdomyolysis, or if the CK criterion necessitating study medication discontinuation is met, the event should be reported as ECI because of their association with lipid-lowering treatments.

8.5 Treatment of Overdose

In this study, an overdose is any dose higher than the amount of study treatment taken outside the treatment assignment.

Sponsor does not recommend specific treatment for an overdose.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

8.6 Pharmacokinetics

PK parameters will not be evaluated in this study.

8.7 Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.8 Future Biomedical Research Sample Collection

Future biomedical research samples will not be collected in this study.

8.9 Planned Genetic Analysis Sample Collection

Planned genetic analysis samples will not be evaluated in this study.

8.10 Biomarkers

Biomarkers are not evaluated in this study.

8.11 Visit Requirements

Visit requirements are outlined in Section 1.3. Specific procedure-related details are provided in Section 8.

8.11.1 Screening (Visit 1)

Approximately 6-7 weeks prior to intervention allocation/randomization, potential participants will be evaluated up to 2 weeks, to determine that they fulfill the entry requirements as set forth in Section 5. Screening procedures may be repeated after consultation with the Sponsor. A participant may be re-screened up to two times. The participant must provide new written informed consent before each time they are re-screened.

A participant who enters screening but is determined not to be eligible to enter the treatment run-in epoch will be considered a screen failure. The investigator may consider re-screening the participant at a later time if he/she believes that the participant's condition has changed and they may potentially be eligible. In this case, a new participant number will be allocated to the participant and he/she will need to re-perform all Visit 1 procedures.

8.11.2 Run-In (Visit 2 and Visit 3)

Visit 2 will be performed approximately 5 weeks prior to randomization (Visit 4).

Dispense run-in intervention to a participant if he/she is eligible for study participation. Participants will be instructed to take 1 tablet from the bottle.

After initiating administration, participant who is determined to be not appropriate by the investigator will be excluded the study as screen failed. If a participant is not eligible for study participation, the investigator should contact with the participant, stop dosing study drug and performing the end of study visit immediately, and a safety follow-up visit by phone-call as appropriate.

NOTE: it is not necessary for screen failed participant who did not start the study intervention to perform follow-up visit after the end of study visit.

Approximately 4 weeks after Visit 2, participants will be scheduled to return for Visit 3. Blood lipid levels (e.g. LDL-C values) and biochemistry test measured at Visit 3 (Week -1) will be used to determine participant's eligibility for intervention allocation/randomization at Visit 4 (Day 1/Week 0).

Participant will be instructed on Chinese Guidelines on Prevention and Treatment of Dyslipidemia in Adults (2016 Edition), and will agree to maintain the diet/exercise regimen throughout the study.

No rescreening will be allowed of participants who discontinue during the run-in phase or fail to be eligible after the run-in phase.

8.11.3 Treatment Period (Visit 4-Visit 6)

After 5-week run-in treatment, participants who archive ≥75% compliance with the run-in medication and have not met their treatment goals for LDL-C according to their risk levels will be eligible for study entry. The site will perform all procedures for Visit 4 and the participant will be randomized. After the all procedures have been completed, the study drugs will be dispensed and the participants should take the treatment at a consistent time each day to promote compliance.

The following visits will be scheduled every 6 weeks for participants to return to perform the study procedures required as per Section 1.3 – SoA.

8.11.4 Discontinued Participants Continuing to be Monitored in the Study

Participants who discontinue study treatment prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

8.11.5 Poststudy (follow-up visit)

Participants will be followed-up by phone approximately 14 days after the last dose of study intervention to determine if any AEs have occurred since the last clinic visit.

9 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the trial. If, after the trial has begun, but prior to any unblinding, changes are made to the study hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the trial. Post hoc exploratory analyses will be clearly identified in the CSR.

9.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Sections 9.2-9.12.

Study Design Overview	A Phase III, Randomized, Double-blind Clinical Trial to Study the Efficacy and Safety of MK-0653C in Chinese participants with Hypercholesterolemia
Treatment Assignment	A double-blind/masking technique will be used. After the run-in period, 180 participants will be randomized in a ratio of 1:1 into the arms of MK-0653C 10/10 mg and atorvastatin 20 mg in Cohort A and 270 participants will be randomized in a ratio of 1:1 into the arms of MK-0653C 10/20 mg and atorvastatin 40 mg in Cohort B. Randomization will be stratified by disease risk category (low, moderate, high, very high) as defined in Section 4.1.
Analysis Populations	Efficacy: Full Analysis Set (FAS) Safety: All Participants as Treated (APaT)
Primary Endpoint	Percent change from baseline in LDL-C at Week 12
Secondary Endpoints	1. Percentage of participants with adverse events. 2. Change from baseline in laboratory parameters and vital signs at each visit 3. Percentage of participants discontinued from study medication
Statistical Methods for Key Efficacy Analyses	The primary hypothesis for each cohort will be evaluated by comparing MK-0653C to atorvastatin on the percent change from baseline in LDL-C using a constrained longitudinal data analysis (cLDA) model.
Statistical Methods for Key Safety Analyses	Counts and percentages of AEs will be provided. P-values and confidence intervals for the incidence of AEs of clinical interest will be estimated using the Miettinen and Nurminen method [Miettinen, Olli and Nurminen, Markku 1985].
Interim Analyses	No interim analyses are planned for this trial.
Multiplicity	The Type-I error rate over the multiple treatment comparisons will be controlled by the Hochberg testing procedure.
Sample Size and Power	A total of approximately 450 participants (180 in Cohort A, 270 in Cohort B) will be randomized.The sample in Cohort A has 93% power to demonstrate the superiority of MK-0653C 10/10 mg over atorvastatin 20 mg at a one-sided 2.5% alpha-level. Similarly, the sample in Cohort B has 95% power to demonstrate the superiority of MK-0653C 10/20 mg over atorvastatin 40 mg at a one-sided 2.5% alpha-level. The overall power to succeed on at least one hypothesis is 99% at a 2.5% alpha-level with 88% power to succeed for both hypotheses.

9.2 Responsibility for Analyses/In-house Blinding

The statistical analysis of the data obtained from this trial will be the responsibility of the Clinical Biostatistics department of the Sponsor.

This trial will be conducted as a double-blind trial under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete.

The Clinical Biostatistics department will generate the randomized allocation schedule(s) for study treatment assignment. Randomization will be implemented in an interactive voice response system/integrated web response system (IVRS/IWRS).

9.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.

9.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated for between-treatment differences are listed below.

9.4.1 Efficacy Endpoints

1. Percent change from baseline in LDL-C at Week12.
2. Percentage of participants meeting the LDL-C treatment goal (see Table 13 in Appendix 7) at Week 12.
3. Percent change from baseline in LDL-C at Week 6.
4. Percent change from baseline in total cholesterol (TC), HDL-C, non-HDL-C, triglyceride (TG), Apo protein (Apo) B at Weeks 6 and 12.

9.4.2 Safety Endpoints

1. Percentage of participants with adverse events.
2. Change from baseline in laboratory parameters and vital signs at each visit.
3. Percentage of participants discontinued from study medication.

9.5 Analysis Populations

9.5.1 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will serve as the primary population for the analysis of efficacy data in this trial. The FAS population for any given endpoint consists of all randomized participants who took at least one dose of study treatment, and have at least one observation of the respective endpoint (baseline or post-baseline) during the treatment period.

Participants will be included in the treatment group to which they are randomized for the analysis of efficacy data using the FAS population. Details on the approach to handling missing data are provided in Section 9.6 Statistical Methods.

9.5.2 Safety Analysis Populations

Analyses of safety data will be performed in the All Participants as Treated (APaT) population, consisting of all randomized participants who received at least one dose of study treatment. Participants will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the APaT population. This will be the treatment group to which they are randomized for all participants except for those who take incorrect study treatment for the entire treatment period. Such participants will be included in the treatment group corresponding to the study treatment actually received. At least one laboratory measurement or vital sign obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

Details on the approach to handling missing data for safety analyses are provided in Section 9.6 Statistical Methods.

9.6 Statistical Methods

Statistical testing and inference for safety analyses are described in Section 9.6.2. Nominal p-values may be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity, sample size, etc. Unless otherwise stated, all statistical tests will be conducted at α=0.05 (2-sided) level.

9.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives.

The study's estimand is a hypothetical estimand that seeks to estimate efficacy as if all participants were to take study medication for 12 weeks.

The estimand consists of the following elements:

- Target population: Participants with hypercholesterolemia (age 18 to 80 years, inclusive), consistent with the study's inclusion/exclusion criteria.
- Variable: Percent change from baseline in LDL-C at Week 12.
- Intercurrent event: Data obtained after discontinuation of treatment are not relevant to this estimand.
- Population level-summary: Difference in variable means comparing randomized treatments (within each cohort).

Analyses will thus exclude measurements collected more than 5 days after the last dose of study treatment.

For the analyses of percent change from baseline in LDL-C at Week 12 in both cohorts, a constrained longitudinal data analysis (cLDA) method proposed by Liang and Zeger will be used [Liang, Kung-Yee and Zeger, Scott L. 2000]. Within each baseline disease risk category (i.e., stratum), this model assumes a common mean across treatment groups at baseline and a different mean for each treatment at each of the post-baseline time points. In this model, the response vector consists of baseline and the values (percent change) observed at each post-baseline time point. Time is treated as a categorical variable so that no restriction is imposed on the trajectory of the means over time. The analysis model will adjust for time and the interaction of time by treatment, and time by baseline disease risk category given in Section 4.1. The treatment difference in terms of mean change from baseline to Week 12 will be estimated and tested from this model. An unstructured covariance matrix will be used to model the correlation among repeated measurements.

Although the baseline measurement is included in the response vector, it is independent of treatment, and hence, the stratum-specific baseline means are constrained to be the same for different treatment groups. Of note, in the event that there are no missing data, the estimated treatment difference from the above cLDA model will be identical to that from a traditional longitudinal ANCOVA model which uses the baseline value as a covariate. However, unlike longitudinal ANCOVA, the cLDA model accounts for variability in the baseline values, thus providing more accurate standard errors and confidence intervals for individual treatment effects. Moreover, this model allows the inclusion of participants who are missing either the baseline or post-baseline measurements, thereby increasing efficiency. Details of the model specification, assumptions, and SAS implementation codes will be provided in the sSAP.

The cLDA method assumes that the mechanism for missing data is missing at random (MAR). Sensitivity analyses will be performed to assess the robustness of the conclusions from the cLDA analyses to departures from MAR. The details will be described in sSAP.

The percentage of participants reaching the LDL-C goals will be analyzed via a logistic regression model with LDL-C goal achievement rate as response variable and treatment and baseline disease risk category given in Section 4.1 as explanatory variables. Odds ratio estimate derived from the logistic regression model and 95% CI will be used to quantify the treatment effect. Imputation of missing data will be based on the marginal univariate normal distributions with means equal to the predicted values and variances equal to the squared standard errors for the predicted values from the cLDA model. Ten sets of imputations of each missing value will be constructed from the cLDA model. Odds ratio estimate derived from the logistic regression model and 95% confidence interval will be used to quantify the treatment effect. Other exploratory endpoints will be evaluated using the same cLDA model, but TG will be transformed by the natural logarithm on account of the non-normality of this endpoint. Geometric mean percent changes from baseline in TG will be calculated based on back-transformation via exponentiation of the model-based LS means and expressed as (geometric mean – 1) multiplied by 100. The treatment differences in geometric mean percent changes from baseline will be calculated based on the difference in the back transformed model-based LS means and 95% confidence intervals (CIs) for the differences will be calculated using the delta method [Wong, P., et al 1999]. Key efficacy analysis is summarized in Table 6.

Table 6 Analysis Strategy for Key Efficacy Variables

Endpoint/Variable	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypotheses			
Percent change from baseline in LDL-C at Week 12	cLDA[†]	FAS	Model-based
[†] Constrained LDA model with terms for treatment, time, the interaction of time by treatment and time by baseline disease risk category.			

9.6.2 Statistical Methods for Safety Analyses

All safety summaries and analyses will consider the cohorts separately (i.e., treatment groups will not be pooled across cohorts).

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests and vital signs.

The analysis of safety results will follow a tiered approach (Table 7). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse events of special interest that are identified a priori constitute “Tier 1” safety endpoints that will be participant to inferential testing for statistical significance with p values and 95% confidence intervals provided for between-group comparisons. Nominal p-values will be provided without any adjustments to account for multiple comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse events (specific terms as well as system organ class terms) and predefined limits of change in laboratory test and vital signs parameters that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 participants in any treatment group exhibit the event; all other adverse events and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse events and predefined limits of change.

Continuous measures such as changes from baseline in laboratory test and vital signs parameters that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters.

Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

For this protocol, the specific Tier 1 adverse events are listed in Table 7. In addition, summary measures of AEs consisting of the percentage of participants with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE, who discontinued due to a drug-related AE, who discontinued due to a serious AE and who discontinued due to a drug-related and serious AE will be considered Tier 2 endpoints. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) will be provided for between-treatment differences in the percentage of participants with events; these analyses will be performed using the Miettinen and Nurminen method (1985), an unconditional, asymptotic method [Miettinen, Olli and Nurminen, Markku 1985].

Table 7 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	p-Value	95% CI for Treatment Comparison	Descriptive Statistics
Tier 1	Hepatitis-related AEs	X	X	X
	Consecutive elevations in ALT ≥3xULN	X	X	X
	Consecutive elevations in AST ≥3xULN	X	X	X
	Consecutive elevations in ALT ≥3xULN or consecutive elevations in AST≥3xULN	X	X	X
	ALT elevation ≥5xULN	X	X	X
	AST elevation ≥5xULN	X	X	X
	ALT elevation ≥5xULN or AST elevation ≥5xULN	X	X	X
	Potential Hy's Law Condition (ALT or AST elevations >3xULN, with ALP <2xULN and TBL ≥2xULN)	X	X	X
	Elevations in CK ≥5xULN with muscle symptoms	X	X	X
	Elevations in CK ≥10xULN	X	X	X
	Elevations in CK ≥10xULN with muscle symptoms	X	X	X
	Elevations in CK ≥10xULN with muscle symptoms that are considered drug-related	X	X	X
Tier 2	Any AE		X	X
	Any Serious AE		X	X
	Any Drug-Related AE		X	X
	Any Serious and Drug-Related AE		X	X
	Discontinuation due to AE		X	X
	Discontinuation due to drug-related AE		X	X
	Discontinuation due to serious AE		X	X
	Discontinuation due to serious and drug-related		X	X
	Specific AEs, SOCs (incidence ≥4 of participants in all of the treatment groups)		X	X
Tier 3	Specific AEs, SOCs (incidence <4 of participants in all of the treatment groups)			X
	Change from baseline in laboratory tests and vital signs			X
SOC=System Organ Class; X = results will be provided.				

9.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The comparability of the treatment groups for each relevant characteristic will be assessed observationally; no statistical hypothesis tests will be performed on these characteristics. The number and percentage of participants screened, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables and baseline characteristics will be summarized by treatment group either by descriptive statistics or categorical tables.

9.7 Interim Analyses

No interim analyses are planned for this trial.

9.8 Multiplicity

The Type-I error rate over the two primary hypotheses will be controlled by the Hochberg procedure [Benjamini, Y. and Hochberg, Y. 1995]. The overall success is determined by a success of at least one hypothesis.

If the one-sided p-values for both primary hypothesis tests are < 0.025, then both tests will be declared successful. Otherwise, if the smaller of the p-values is <0.0125, then only the hypothesis test associated with the smaller p-value will be declared successful.

9.9 Sample Size and Power Calculations

A total of approximately 450 participants (180 in Cohort A, 270 in Cohort B) will be randomized. The power computation has been performed conservatively based on the number of participants expected to have LDL-C data at Week 12. Assuming a drop-out rate of 10%, 162 participants (81 per arm) in Cohort A and 242 participants (121 per arm) in Cohort B will be available for the power calculation. The sample in Cohort A has a 93% power to demonstrate the superiority of MK-0653C 10/10 mg over atorvastatin 20 mg at a one-sided 2.5% alpha-level. The half-width of the 95% confidence interval for the between-treatment difference is expected to be 7.0%. Similarly, the sample in Cohort B has a 95% power to demonstrate the superiority of MK-0653C 10/20 mg over atorvastatin 40 mg at a one-sided 2.5% alpha-level. The half-width of the 95% confidence interval for the between-treatment difference is is expected to be 5.7%. The overall power to success on at least one hypothesis is 99% at a 2.5% alpha-level with 88% power to succeed for both hypotheses. If only one hypothesis is successful according to Hochberg procedure, the sample in Cohort A will result in a power of 88% and the sample in Cohort B will result in a power of 91% at 1.25% alpha-level. The power and sample sizes are based on the following assumptions: the treatment difference in percent changes from baseline in LDL-C at Week 12 are 12.3% and 10.5%, and unconditional standard deviations are 22% and 23% for Cohorts A and B, respectively, according to P162 results from the ANCOVA model.

The safety power table displays a range of AE rates and the possible difference that can be detected with the sample size of the study at 90% and 80% power is shown in Table 8. All calculations are based on 2-sided α=0.05 significance level.

Table 8 Safety Power Calculation

AE rate in Atorvastatin 20 mg or 40 mg Group	Percentage Point Difference in Cohort A (MK-0653C 10/10 mg- Atorvastatin 20 mg) Power of 80% (90%)	Percentage Point Difference in Cohort B (MK-0653C 10/20 mg- Atorvastatin 40 mg) Power of 80% (90%)
1%	10.3 (12.2)	8.2 (10.0)
2%	11.4 (13.5)	9.2 (11.1)
3%	12.3 (14.6)	9.9 (11.9)
AE = adverse event		

9.10 Subgroup Analyses

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated within each category of the following classification variables:

- Age category (< 65, ≥65 years)
- Gender (male, female)
- Baseline LDL-C (≤ or > median)
- Disease risk Category based on LDL-C (as in Section 4.1)

9.11 Compliance (Medication Adherence)

As part of the routine recording of the amount of study treatment taken by each participant, the number of tablets remaining in trial packaging will be counted, reviewed, and recorded at regular intervals. These results will be used to calculate participant compliance.

A day within the trial will be considered an "On-Therapy" day if the participant in Cohort A takes two tablets OR the participant in Cohort B takes three tablets every day: 1 (for Cohort A) or 2 (for Cohort B) tablets from the bottle and 1 tablet from the blister, as described in Section 8.1.8.

For each participant, percent compliance will then be calculated using the following formula:

$$\text{Compliance (\%)} = \frac{\text{Number of days on therapy}}{\text{Number of days in the double-blind treatment period}} \text{ x100.}$$

The "Number of days in the double-blind treatment period" is the total number of days from the first dose of study medication to the last dose of study medication.

Summary statistics will be provided on percent compliance by treatment group for the FAS population.

9.12 Extent of Exposure

The Extent of Exposure to study treatment will be evaluated by summary statistics for the "Number of Days on Therapy" by treatment group.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Code of Conduct for Clinical Trials

Merck Sharp and Dohme Corp., a subsidiary of Merck & Co., Inc. (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (eg, International Council for Harmonisation Good Clinical Practice [ICH-GCP]) and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD irrespective of the party (parties) employed for their execution (eg, contract research organizations, collaborative research efforts). This Code is not intended to apply to trials that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy, and/or pharmacokinetic or pharmacodynamic indices of MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (ie, participant population, duration, statistical power) must be adequate to address the specific purpose of the trial. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel to assess the ability to successfully conduct the trial.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if fraud, scientific/research misconduct, or serious GCP-noncompliance is suspected, the issues

are investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the prespecified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing, in such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All clinical trials will be reviewed and approved by an IRB/IEC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the ethics committee prior to implementation, except changes required urgently to protect participant safety that may be enacted in anticipation of ethics committee approval. For each site, the ethics committee and MSD will approve the participant informed consent form.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible. Unless required by law, only the investigator, Sponsor (or representative), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

Clinical trials are time- and labor-intensive. It is MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll participants in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review to identify potentially eligible participants.

B. Clinical Research Funding

Informed consent forms will disclose that the trial is sponsored by MSD and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local ethics committee may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, all publications resulting from MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (eg, to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

Investigators will be expected to review MSD's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

10.1.2 Financial Disclosure

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.1.3 Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.3.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the IRB, IEC, or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

10.1.3.2 Confidentiality of Participant Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/IEC, or regulatory authority representatives may consult and/or copy study documents to verify worksheet/CRF data. By signing the consent form, the participant agrees to this process. If study documents will be photocopied during the process of verifying worksheet/CRF information, the participant will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all participant data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

10.1.3.3 Confidentiality of IRB/IEC Information

The Sponsor is required to record the name and address of each IRB/IEC that reviews and approves this study. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

10.1.4 Committees Structure

Not applicable for this study.

10.1.5 Publication Policy

The results of this study may be published or presented at scientific meetings. The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

If publication activity is not directed by the Sponsor, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.6 Compliance with Study Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. MSD, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow participants to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and study site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive, or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this study or its results to those registries.

10.1.7 Compliance with Law, Audit, and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP: Consolidated Guideline and other generally accepted standards of GCP); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical study.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by MSD, is provided in this appendix under the Code of Conduct for Clinical Studies.

The investigator agrees not to seek reimbursement from participants, their insurance providers, or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this study.

The investigator agrees to provide the Sponsor with relevant information from inspection observations/findings to allow the Sponsor to assist in responding to any citations resulting from regulatory authority inspection and will provide the Sponsor with a copy of the proposed response for consultation before submission to the regulatory authority.

Persons debarred from conducting or working on clinical studies by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

10.1.8 Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator or qualified designee is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the study site upon request for inspection, copying, review, and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor or any regulatory authorities as a result of an audit or inspection to cure deficiencies in the study documentation and worksheets/CRFs.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data review and verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.9 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. The investigator/institution should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's participants. Source documents and data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator/institution may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

10.1.10 Study and Site Closure

The Sponsor or its designee may stop the study or study site participation in the study for medical, safety, regulatory, administrative, or other reasons consistent with applicable laws, regulations, and GCP.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that study site's IRB/IEC.

10.2 Appendix 2: Clinical Laboratory Tests

- The tests with marker of * listed in Table 9 will be performed by the local laboratory at Visit 1.

- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Table 9 Protocol-required Laboratory Assessments

Laboratory Assessments	Parameters			
Hematology*	Platelet Count RBC Count Hemoglobin Hematocrit	RBC Indices: MCV MCH %Reticulocytes		WBC count with Differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Chemistry*	Blood Urea Nitrogen (BUN)	Potassium	Aspartate Aminotransferase (AST)/ Serum Glutamic-Oxaloacetic Transaminase (SGOT)	Total bilirubin (and direct bilirubin, if total bilirubin is elevated above the upper limit of normal)
	Albumin	CK (CPK)	Chloride	eGFR
	Creatinine	Sodium Calcium Potassium Phosphorous Bicarbonate	Alanine Aminotransferase (ALT)/ Serum Glutamic-Pyruvic Transaminase (SGPT)	Total Protein
	Glucose (fasting)	Uric acid	Alkaline phosphatase (ALP)	γ-glutamyl transferase
Lipid Panel A*	LDL-C	HDL-C non-HDL-C	total cholesterol (TC)	Triglyceride (TG)
Routine Urinalysis*	Specific gravity	pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick		Microscopic examination (if blood or protein is abnormal)
Apolipoprotein Evaluations	• Apolipoprotein B (Apo B)			
Pregnancy test	• Urine pregnancy test (urine hCG) will be determined at the site (as needed for WOCBP). • Serum β-hCG test will be required if urine pregnancy result is positive.			
Other Laboratory Tests	• Follicle-stimulating hormone (FSH): only applicable for perimenopausal women. • Thyroid stimulating hormone (TSH), fT4			

Laboratory Assessments	Parameters
NOTES: * Laboratory tests results received within 4 weeks prior to screening visit is acceptable as screening test to check the eligibility.	

The investigator (or medically qualified designee) must document their review of each laboratory safety report.

All lipid evaluations results will be blinded to participants and to study team once the participant is centrally randomized. No attempts could be made to have local evaluation of the participant's lipid levels once they have successfully entered the double blind treatment phase. The investigator will not be blinded to laboratory safety results. Emergency treatment code breaks should only be undertaken when it is essential to treat the participant safely and efficaciously. Most often, study drug discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. In case that emergency unblinding is required, investigator should start the processed after consultation and discussion with sponsor.

10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study intervention.

- NOTE: For purposes of AE definition, study intervention (also referred to as Sponsor's product) includes any pharmaceutical product, biological product, vaccine, diagnostic agent, or protocol specified procedure whether investigational or marketed (including placebo, active comparator product, or run-in intervention), manufactured by, licensed by, provided by, or distributed by the Sponsor for human use in this study.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator.

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.

- For all reports of overdose (whether accidental or intentional) with an associated AE, the AE term should reflect the clinical symptoms or abnormal test result. An overdose without any associated clinical symptoms or abnormal laboratory results is reported using the terminology "accidental or intentional overdose without adverse effect."

Events NOT meeting the AE definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

- Surgery planned prior to informed consent to treat a pre-existing condition that has not worsened.

- Refer to Section 8.4.6 for protocol-specific exceptions.

10.3.2 Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met.

An SAE is defined as any untoward medical occurrence that, at any dose:

a. **Results in death**

b. **Is life-threatening**

- The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. **Requires inpatient hospitalization or prolongation of existing hospitalization**

- Hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not an SAE. A pre-existing condition is a clinical condition that is diagnosed prior to the use of an MSD product and is documented in the participant's medical history.

d. **Results in persistent or significant disability/incapacity**

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. **Is a congenital anomaly/birth defect**

- In offspring of participant taking the product regardless of time to diagnosis.

f. **Other important medical events**

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Additional Events Reported

Additional events that require reporting

In addition to the above criteria, AEs meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor.

- Is a cancer

- Is associated with an overdose

10.3.4 Recording AE and SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

- The investigator will record all relevant AE/SAE information on the AE CRFs/worksheets at each examination.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the AE CRF page.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be blinded on the copies of the medical records before submission to the Sponsor.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

- An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

- The investigator will make an assessment of intensity for each AE and SAE (and other reportable safety event) reported during the study and assign it to 1 of the following categories:

  - Mild: An event that is easily tolerated by the participant, causing minimal discomfort, and not interfering with everyday activities (for pediatric studies, awareness of symptoms, but easily tolerated).

  - Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities (for pediatric studies, definitely acting like something is wrong).

  - Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category used for rating the intensity of an event; and both AE and SAE can be assessed as severe (for pediatric studies, extremely distressed or unable to do usual activities).

- **Assessment of causality**

- Did the Sponsor's product cause the AE?

- The determination of the likelihood that the Sponsor's product caused the AE will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test product and the AE based upon the available information.

- **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the AE:

  - **Exposure:** Is there evidence that the participant was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?

  - **Time Course:** Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?

  - **Likely Cause:** Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors.

  - **Dechallenge:** Was the Sponsor's product discontinued or dose/exposure/frequency reduced?

    - If yes, did the AE resolve or improve?

    - If yes, this is a positive dechallenge.

    - If no, this is a negative dechallenge.

    (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the study is a single-dose drug study; or (4) Sponsor's product(s) is/are only used 1 time.)

  - **Rechallenge:** Was the participant re-exposed to the Sponsor's product in this study?

    - If yes, did the AE recur or worsen?

    - If yes, this is a positive rechallenge.

    - If no, this is a negative rechallenge.

    (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose drug study; or (3) Sponsor's product(s) is/are used only 1 time.)

NOTE: IF A RECHALLENGE IS PLANNED FOR AN AE THAT WAS SERIOUS AND MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE PARTICIPANT THEN THE RECHALLENGE MUST BE APPROVED IN

ADVANCE BY THE SPONSOR CLINICAL DIRECTOR, AND IF REQUIRED, THE IRB/IEC.

- **Consistency with study intervention profile:** Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?

- The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.

- Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).

  - Yes, there is a reasonable possibility of Sponsor's product relationship:

    - There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.

  - No, there is not a reasonable possibility of Sponsor's product relationship:

    - Participant did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a participant with overdose without an associated AE.)

- For each AE/SAE, the investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

- The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

- New or updated information will be recorded in the CRF.

- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.5 Reporting of AEs, SAEs, and Other Reportable Safety Events to the Sponsor

AE, SAE, and other reportable safety event reporting to Sponsor via electronic data collection tool

- The primary mechanism for reporting to the Sponsor will be the electronic data collection (EDC) tool.
    - Electronic reporting procedures can be found in the EDC data entry guidelines (or equivalent).
    - If the electronic system is unavailable for more than 24 hours, then the site will use the paper AE Reporting form.
        - Reference Section 8.4.1 for reporting time requirements.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the EDC tool has been taken off-line, then the site can report this information on a paper SAE form or by telephone (see next section).
- Contacts for SAE reporting can be found in the Investigator Study File Binder (or equivalent).

SAE reporting to the Sponsor via paper CRF

- If the EDC tool is not operational, facsimile transmission or secure e-mail of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

- Contacts and instructions for SAE reporting and paper reporting procedures can be found in the Investigator Study File Binder (or equivalent).

10.4 Appendix 4: Device Events, Adverse Device Events, and Medical Device Incidents: Definitions, Collection, and Documentation

Not applicable.

10.5 Appendix 5: Contraceptive Guidance and Pregnancy Testing

10.5.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

  For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

  Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonhormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.5.2 Contraception Requirements

Female Participants

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
• Progestogen-only subdermal contraceptive implant[b,c] • Intrauterine hormone-releasing system (IUS)[c,d] • Intrauterine device (IUD) • Bilateral tubal occlusion
• Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence • Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
1. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. 2. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. a) IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, sympothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM). - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

10.5.3 Pregnancy Testing

WOCBP should only be included after a negative highly sensitive urine or serum pregnancy test and in accordance with local requirements. This test should be repeated a maximum of 24 hours before the first dose.

Following initiation of treatment, pregnancy testing will be performed at scheduled visits during the treatment period, and as required locally.

Additional pregnancy testing will be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

10.6 Appendix 6: Collection and Management of Specimens for Future Biomedical Research

Not applicable.

10.7 Appendix 7: Country-specific Requirements

2016 Chinese guidelines for the management of dyslipidemia in adults

Joint committee for guideline revision

National Expert Committee on Cardiovascular Diseases, National Center for Cardiovascular Diseases

Chinese Society of Cardiology, Chinese Medical Association

Chinese Diabetes Society, Chinese Medical Association

Chinese Society of Endocrinology, Chinese Medical Association

Chinese Society of laboratory Medicine, Chinese Medical Association

Writing group members

Group leader: PPD

Main authors: PPD

Members: Listed in Supplement 3

Academic secretary: PPD

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Keywords: Adults; Chinese guidelines; Dyslipidemia

Abbreviations

ACS: acute coronary syndrome

ALT: alanine aminotransferase

Apo: apolipoprotein

ASCVD: atherosclerotic cardiovascular disease

AST: aspartate aminotransferase

BMI: body mass index

CKD: chronic kidney disease

CM: chylomicron

ESDR: end-stage renal disease

FDA: Food and Drug Administration

FH: familial hypercholesterolemia

GFR: glomerular filtration rate

HDL-C: high-density lipoprotein cholesterol

IDL: intermediate-density lipoprotein

LDL-C: low-density lipoprotein cholesterol

LP: lipoprotein

Lp (a): lipoprotein(a)

LPL: lipoprotein lipase

Ox-LDL: oxidized low-density lipoprotein

PCI: percutaneous coronary intervention

PCSK: proprotein convertase subtilisin/Kexin

PPARα: peroxisome proliferator activated receptor α

sLDL: small and low density lipoprotein

TC: total cholesterol

TG: triglyceride

HeFH: heterozygous familial hypercholesterolemia

HMG-CoA: 3-hydroxy-3-methylglutaryl-coenzyme A

HoFH: homozygous familial hypercholesterolemia

TIA: transient ischemic attack

TLC: therapeutic lifestyle changes

VLDL-C: very-low-density lipoprotein cholesterol

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1 Introduction

Over the last 30 years, the blood lipid level in the Chinese population has gradually increased, and the incidence of dyslipidemia has significantly increased. A nationwide survey in 2012 showed that the average serum total cholesterol (TC) value in adults was 4.50 mmol/L and that the prevalence of hypercholesterolemia was 4.9%; the average value of triglyceride (TG) was 1.38 mmol/L, and the prevalence of hypertriglyceridemia was 13.1%; the average value of high-density lipoprotein cholesterol (HDL-C) was 1.19 mmol/L, and the prevalence of HDL-C hypolipidemia was 33.9%.[1] The overall prevalence of dyslipidemia among Chinese adults reached 40.4%, which has substantially increased since 2002. The increase of serum cholesterol level in the population will increase by approximately 9.2 million cases of cardiovascular events in China between 2010 and 2030.[2] The prevalence of hypercholesterolemia among Chinese children and adolescents is also significantly increasing,[3] suggesting that the development of dyslipidemia and the relevant disease burdens in Chinese adults will continue to increase.

Dyslipidemia characterized by the increase of low-density lipoprotein cholesterol (LDL-C) or TC is an important risk factor for atherosclerotic cardiovascular diseases. The reduction of LDL-C levels can significantly decrease the development and mortality risks of atherosclerotic cardiovascular diseases.[4] Other types of dyslipidemia (e.g., increases of TG or decreases of HDL-C) are also correlated with the increase of developing atherosclerotic cardiovascular diseases.[5–7]

The effective control of dyslipidemia has important significance for the management of atherosclerotic cardiovascular diseases in China. Encouraging people to adopt a healthy lifestyle is the basic strategy for managing dyslipidemia and atherosclerotic cardiovascular diseases. The focus of dyslipidemia management is to increase the awareness, treatment, and control rates of dyslipidemia. Although the awareness and treatment rates of Chinese adult dyslipidemia patients have increased over recent years,[8] they remain at low levels. Therefore, the management work of dyslipidemia urgently needs to be strengthened.

In 2007, a joint committee of multidisciplinary experts together formulated the “Chinese Guidelines for the Management of Dyslipidemia in Adults” (referred to as "Guidelines" hereafter). Based on the full adoption of epidemiological and clinical study results from the Chinese population and combined with international study results and guideline recommendations, the “Guidelines” proposed recommendations that were more appropriate for the management of dyslipidemia in the Chinese population. These recommendations had important guiding functions for the management of dyslipidemia in China.[9]

Since 2007, more clinical study results have further validated the effectiveness and safety of cholesterol-lowering treatments on the primary and secondary prevention of atherosclerotic cardiovascular diseases. Many international academic institutions successively updated or formulated new management guidelines for dyslipidemia. During this period, studies in the clinical blood lipid field in China made significant progress. Prospective cohort studies on the Chinese population obtained new 20-year follow-up data. Based on the 10-year overall risk assessment program recommended by the 2007 Guidelines, the lifetime risk assessment program was proposed.[10]

In November 2013, supported by the Department of Diseases Control of the National Health and Family Planning Commission of the People’s Republic of China (NHFPC), the National Expert Committee on Cardiovascular Diseases of the National Center for Cardiovascular Diseases, the Chinese Society of Cardiology of Chinese Medical Association, the Chinese Diabetes Society of the Chinese Medical Association, the Chinese Society of Endocrinology of the Chinese Medical Association, and the Chinese Society of Laboratory Medicine of the Chinese Medical Association formed a joint committee to revise the blood lipid guidelines. These committee members extensively collected core issues to be addressed by the new guidelines. After discussion, 17 core issues across 4 aspects (the overall principle of guideline revisions, the overall cardiovascular risk assessment, the goals of lipid-lowering treatment, and lipidlowering treatments for special populations) were eventually confirmed. The guideline-revision working group targeted these core issues to formulate specific literature retrieval and evaluation strategies as well as comprehensively evaluate and screen the relevant literature. The literature retrieval databases included the Chinese Biomedicine Literature Database (CBM), Wanfang Data Knowledge Service Platform, China National Knowledge Infrastructure (CKNI), the American Biomedical Literature Database (PubMed), and the Dutch Excerpta Medica database (EMBASE). In addition, new data from long-term cohort studies in China were used to conduct targeted analyses. The recommendations and suggestions proposed by the revised guidelines were developed after repeated discussion among multidisciplinary experts based on a systemic assessment. When the expert opinions disagreed, the consensus of the majority of experts was accepted based on a full consideration of the different opinions.

The guideline revision referenced the standard procedures developed by the World Health Organization (WHO) and the Chinese Medical Association’s clinical guidelines.[11] During the process of guideline revision, the National Center for Cardiovascular Diseases raised funds to avoid conflicts of interest with vendors.

The definitions of the recommendation classifications in the "Guidelines" reference the definitions in the relevant European and American blood lipid guidelines.[12,13] The specific descriptions are shown below:

Class I: Manipulations or treatments that have been confirmed confirmed/unanimously recognized as beneficial, useful, and effective are recommended.

Class II: Manipulations or treatments that still have contradictions or different opinions according to useful/effective evidence.

Class IIa: Relevant evidence/opinions tend to be useful/effective. The application of these manipulations or treatments is reasonable.

Class IIb: Relevant evidence/opinions cannot be fully confirmed as useful/effective. Its application can be considered.

Class III: It has been confirmed/consistently recognized as useless/ineffective and manipulations or treatments might be harmful in some cases. Its application is not recommended.

The definitions of the level of evidence in the "Guidelines" are described below:

Evidence level A: Evidence based on many randomized clinical trials or meta-analyses.

Evidence level B: Evidence based on single randomized clinical trials or many non-randomized controlled studies.

Evidence level C: Only expert consensus opinion or based on the results of small-scale studies, retrospective studies, or registry studies.

2 Blood lipids and lipoproteins

Highlights: Blood lipids are the collective term for cholesterol, TG, and lipoids (e.g., phospholipids) in the serum. Blood lipids that have a close clinical association are primarily cholesterol and TG. Cholesterol in the human body primarily exists in the forms of free cholesterol and cholesteryl ester. TG is formed by the fatty acid esterification of the three hydroxyl groups in the glycerol molecule. Blood lipids are insoluble in water, and they can be dissolved in water after binding to special proteins, lipoproteins (Apo), to form lipoproteins that are transferred to tissues to be metabolized. Lipoproteins are classified as CM, VLDL, IDL, LDL, HDL, and Lp (a).

Blood lipids are the collective term for cholesterol, TG, and lipoids (e.g., phospholipids) in serum. Blood lipids that have close clinical association are primarily cholesterol and TG. The blood lipids that have a close clinical association are primarily cholesterol and TG. Cholesterol in the human body primarily exists in the forms of free cholesterol and cholesteryl ester. TG is formed by the fatty acid esterification of the three hydroxyl groups in the glycerol molecule. Blood lipids are insoluble in water, but they can be dissolved in water

after binding to special proteins, apolipoproteins (Apo), to form lipoproteins that are transferred to tissues to be metabolized.

Lipoproteins are classified as chylomicrons (CM), verylow-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), LDL-C, and HDL-C. One type of lipoprotein is known as lipoprotein (a) (Lp[a]). The physical properties, main components, sources, and functions of lipoproteins are listed in Table 10.[14,15]

Table 10 The Characteristics and Functions of Lipoproteins

Classifi-cation	Hydration density, g/mL	Particle diameter, nm	Main component	Major apolipoproteins	Sources	Functions
CM	< 0.950	80-500	TG	B48, A1, A2	Synthesis in small intestine	Transfers TG and cholesterol in food from small intestine to other tissues
VLDL	0.950-1.006	30-80	TG	B100, E, Cs	Synthesis in liver	Transfers endogenous TG to the peripheral tissues to release free fatty acids after lipase hydrolysis
IDL	1.006-1.019	27-30	TG, cholesterol	B100, E	Formed after lipase hydrolysis of TG in VLDL	Belongs to the LDL-C precursor; some are metabolized in liver
LDL-C	1.019-1.063	20-27	Cholesterol	B100	Formed after lipase hydrolysis of TG in VLDL and IDL	The major carrier of cholesterol, taken-up (mediated by LDL-C receptors) and used by the peripheral tissues. Directly associated with ASCVD
HDL-C	1.063-1.210	8-10	Phospho-lipid, cholesterol	A1, A2, Cs	Primarily synthesized by liver and small intestine	Promotes the removal of cholesterol from the peripheral tissues. Transfers cholesterol to liver or other tissues for re-distribution. HDL-C is negatively correlated with ASCVD
Lp(a)	1.055-1.085	26	Cholesterol	B100, (a)	Complex formed by lipoprotein (a) and LDL-C through disulfide bonds in liver	Might be associated with ASCVD

ASCVD: atherosclerotic cardiovascular disease; CM: chylomicron; HDL-C: high-density lipoprotein cholesterol; IDL: intermediate-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; Lp (a): lipoprotein(a); TG: triglyceride; VLDL: very-low-density lipoprotein cholesterol.

2.1 CM

CM is the largest lipoprotein particle in the blood. The major component is TG, which accounts for approximately 90% of CM. The density is low. Blood collected after healthy individuals fast for 12 h shows that no CM exists in serum. After a meal or under certain pathological conditions when the blood contains a large amount of CM, the appearance of the blood shows a white turbidity. When the serum tube is stored at 4°C overnight, CM will float to the upper layer of the serum to aggregate, and the shape is like butter. This simple method is used to examine the presence of CM.

2.2 VLDL

VLDL is synthesized by the liver. Its TG content accounts for approximately 55% of its mass. VLDL and CM are collectively termed as "TG-rich lipoproteins". In serum without the presence of CM, the TG concentration can reflect the amount of VLDL. Because the VLDL molecule is smaller than CM, the serum after fasting for 12 h is clear and transparent. When the TG level in fasting serum is > 3.4 mmol/L (300 mg/dL), the serum will exhibit emulsion luster until it becomes turbid.

2.3 LDL-C

LDL-C is converted from VLDL and IDL (of which TG forms LDL-C after lipase hydrolysis). The LDL-C particle contains approximately 50% cholesterol, and it is the lipoprotein in blood with the highest cholesterol content; therefore, it is called a "cholesterol-rich" lipoprotein. In simple hypercholesterolemia, the increase of the cholesterol concentration parallels the serum LDL-C level. Because LDL-C particles are small even when the concentration of LDL-C is high, the serum will not become turbid. More than 95% of the Apo in LDL-C is Apo B100. Based on particle size and different density levels, LDL-C can be divided into different sub-components. LDL-C transfers cholesterol to the peripheral tissues. Most LDL-C is catabolized by hepatocytes and extrahepatic LDL-C receptors.

2.4 HDL-C

HDL-C is primarily synthesized by the liver and small intestine. HDL-C is the smallest particle lipoprotein. Lipid and protein portions almost account for half of the mass. The Apo in HDL-C is primarily Apo A1. HDL-C represents a group of heterogeneous lipoprotein because the quantity and quality of lipids, Apo, enzymes, and lipid transfer proteins in HDL-C particles are different. Using different separation methods, HDL-C can be divided into different sub-components. These HDL-C sub-components have different shapes, densities, particle sizes, electric charges, and anti-atherosclerotic characteristics. HDL-C transfers cholesterol from the peripheral tissues (including atherosclerotic plaques) to the liver for recycling or excretion in the form of cholic acid. This process is called "reverse cholesterol transport".

2.5 Lp (a)

Lp (a) represents a group of special lipoprotein discovered using immunization methods. The lipid components of Lp (a) are similar to those of LDL-C. In addition to one molecule of Apo B100, however, its Apo fraction also contains one molecule of Apo (a). Little is known about the exact mechanisms of Lp (a) synthesis and catabolism.

2.6 Non-HDL-C

Non-HDL-C refers to the sum of cholesterol in other lipoproteins except for HDL-C. The calculation formula is non-HDL-C = TC - HDL-C. As a secondary target of lipidlowering treatment during the management of atherosclerotic cardiovascular disease (ASCVD) and the high-risk population, non-HDL-C is applicable for individuals with LDL-C levels that are not high or have already reached the treatment goal when the TG level is 2.3-5.6 mmol/L (200-500 mg/dL). International blood lipid guidelines recommend using non-HDL-C as the marker for the primary and secondary prevention of ASCVD.[16]

3 Blood lipid examination

Highlights: The basic items in clinical blood lipid examination are TC, TG, LDL-C, and HDL-C. The clinical application values of other blood lipid items (e.g., Apo A1, Apo B, and Lp [a]) have also received increasing attention.

The basic items in clinical blood lipid detection are TC, TG, LDL-C, and HDL-C. The clinical application values of other blood lipid items (e.g., Apo A1, Apo B, and Lp [a]) have also received increasing attention.[17]

3.1 TC

TC refers to the total amount of cholesterol in the various lipids in the blood. The major factors affecting the TC level include the following:

(1) Age and gender. TC levels usually increase with age; however, it no longer increases or decreases after 70 years old. The level of TC in young and middle-aged women is lower than that in men. The TC level in women after menopause is higher than that in age-matched men.

(2) Eating habits. Long-term high cholesterol and highsaturated fatty acid intake can increase TC.

(3) Genetic factors. Mutations in lipoprotein metabolismrelated enzymes or receptor genes are the major causes of significant increases in TC.

The risk assessment and prediction values of TC on ASCVD are not as accurate as those of LDL-C. The calculation of non-HDL-C and VLDL-C should detect TC.

3.2 TG

TG level is affected by the effects of genetic and environmental factors and is associated with race, age, gender, and living habits (e.g., diet and exercise). Unlike TC, TG shows large variations within and between individuals. The TG level in the same individual is influenced by factors such as diet and different time points. Therefore, when the same individual receives multiple detections, the TG values might have significant differences. The serum TG levels in the population show an obvious positive skew.

Mild-to-moderate increases in TG usually reflect increases in VLDL and its remnant particles (VLDL with smaller particles). These remnant lipoproteins might directly cause atherosclerosis because the particles become smaller. However, most studies suggest that the increase of TG causes atherosclerosis through the influence of the structures of LDL-C or HDL-C. Survey data indicate that people with mild-to-moderate increases in serum TG levels are at increased risk for the development of coronary heart disease.[18] Severely increased TG is usually accompanied by acute pancreatitis.

3.3 LDL-C

Cholesterol accounts for approximately 50% of LDL-C. Therefore, the LDL-C concentration basically reflects the total amount of LDL-C in the blood. The factors that affect TC can also affect the LDL-C level. The increase of LDL-C is a major risk factor for the initiation and progression of atherosclerosis.[12,16] LDL-C enters into the vascular wall through the vascular endothelia. LDL-C retained in the subcutaneous layer is modified into oxidized-LDL (Ox-LDL). After being phagocytized by macrophages, Ox-LDL forms a foam cell; the latter continues to increase and fuse to become the lipid core of atherosclerotic plaques. Although the pathology of atherosclerosis exhibits chronic inflammatory reaction features, LDL-C might be the basic element for the initiation and maintenance of this chronic inflammatory reaction. Under general conditions, LDL-C parallels TC; however, the TC level is also influenced by the HDL-C level. Therefore, it is better to use LDL-C as the assessment indicator for the risk of ASCVD.

3.4 HDL-C

HDL-C can transport cholesterol in peripheral tissues such as the vascular wall to the liver for catabolism (i.e., reverse cholesterol transport). HDL-C can reduce cholesterol deposition in the vascular wall to as an anti-atherosclerosis function. Because the cholesterol content in HDL-C is stable, its current cholesterol content is primarily measured to indirectly understand HDL-C levels in the blood.

Genetic factors also significantly influence the level of HDL-C. With the significant reduction of serum TC, people with severe malnutrition have decreased HDL-C. The HDL-C levels of obese people are also lower. Smoking can reduce HDL-C. Diseases such as diabetes, hepatitis, and cirrhosis can be accompanied by low HDL-C; however, exercise and a small amount of alcohol increase HDL-C. Much epidemiological data indicate that serum HDL-C levels are negatively correlated with the incidence of ASCVD.[19]

3.5 Apo A1

The Apo A1 levels in the normal population are primarilywithin the range of 1.2-1.6 g/L. The levels in women are slightly higher than those in men. The protein component of HDL-C particles (i.e., apolipoprotein) accounts for approximately

50% of its mass. In proteins, Apo A1 accounts for approximately 65%-75%, whereas little Apo A1 is present in other lipoproteins. Therefore, serum Apo A1 reflects the HDL-C level. It is positively correlated with HDL-C levels and has a similar clinical significance.

3.6 Apo B

The Apo B levels in the healthy population are primarily within the range of 0.8-1.1 g/L. Under normal conditions, LDL-C, IDL, VLDL, and Lp (a) particles have one molecule of Apo B. Because LDL-C particles account for the majority of these molecules, approximately 90% Apo B is distributed in LDL-C. There are two types of Apo B: Apo B_{48} and Apo B_{100}. The former is primarily present in CM, whereas the latter is primarily present in LDL-C. Except for special instances, the Apo B routinely measured in clinics usually refers to Apo B_{100}.

Serum Apo B primarily reflects the LDL-C level and is positively correlated with the serum LDL-C level. These two types have a similar clinical significance. In a few cases, Apo B hyperlipidemia and normal LDL-C concentrations can occur, suggesting the presence of increased small and dense LDL (sLDL) in the blood. During hypertriglyceridemia (high VLDL), sLDL (LDL pattern B) increases. However, compared with large and light LDL (LDL pattern A), sLDL particles have a high Apo B content and less cholesterol; therefore, this condition when LDL-C is not high but serum Apo B increases is called “Apo B hyperlipidemia”. This situation reflects the increase of LDL pattern B. Therefore, the measurement of ApoB and LDL-C together can help clinical diagnoses.

3.7 Lp (a)

Serum Lp (a) concentration is primarily associated with genetics. Gender, age, body weight, and most cholesterollowering drugs do not often affect this concentration. The Lp (a) level in the healthy population shows an obvious skew. Although the level in individuals can reach above 1,000 mg/L, the level in 80% healthy individuals is less than 200 mg/L. Usually, 300 mg/L is used as the cutoff point. People with levels higher than this cutoff are at a significantly increased risk for coronary heart disease, suggesting that Lp (a) causes atherosclerosis. However, clinical evidence is lacking.[20] Furthermore, an increase of Lp (a) can also be observed during various acute phase responses, nephrotic syndrome, diabetic nephropathy, pregnancy, and the administration of growth hormone. After all types of stress increase are excluded, Lp (a) is considered as an independent risk factor for ASCVD.

The expression unit of the values of all blood lipid measurement items is mmol/L according to the national standard of China. Some other countries use mg/dL. The conversion coefficients are: TC, HDL-C, LDL-C: 1 mg/dL = 0.0259 mmol/L; and TG: 1 mg/dL = 0.0113 mmol/L.

4 Appropriate levels and abnormal cutoff points

Highlights: The appropriate levels and abnormal cutoff points of blood lipids are primarily applicable for the target population regarding the primary prevention of ASCVD.

The major hazard of dyslipidemia is the increase of the risk for developing ASCVD. The "Guidelines" recommend the appropriate levels and abnormal cutoff points for the blood lipid components in the Chinese population (Table 11) based on the results of many long-term observatory studies concerning the risk of developing ASCVD in Chinese populations with different blood lipid levels, including the independent influence of different blood lipid levels with regard to the cumulative risk for developing ASCVD in the study populations in 10 and 20 years. In addition, the recommendations and the references for the appropriate levels of blood lipid components in the many blood-lipid-related guidelines worldwide are referenced.[12,16,21,22] Importantly, these appropriate levels and abnormal cutoff points of blood lipids are primarily applicable for the target population regarding the primary prevention of ASCVD.

Table 11 The Appropriate Levels and Abnormal Stratified Standards of Blood Lipids for the Primary Prevention Population of ASCVD in China [mmol/L (mg/dL)]

	TC	LDL-C	HDL-C	Non-HDL	TG
Ideal level		< 2.6 (100)		< 3.4 (130)	
Appropriate level	< 5.2 (200)	< 3.4 (130)		< 4.1 (160)	< 1.7 (150)
Marginal increase	≥ 5.2 (200) and < 6.2 (240)	≥ 3.4 (130) and < 4.1 (160)		≥ 4.1 (160) and < 4.9 (190)	≥ 1.7(150) and < 2.3 (200)
Increase	≥ 6.2 (240)	≥ 4.1 (160)		≥ 4.9 (190)	≥ 2.3 (200)
Decrease			< 1.0 (40)		

ASCVD: atherosclerotic cardiovascular disease; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride.

5 Classification of dyslipidemia

Highlights: The classification of dyslipidemia is complicated. The simplest methods include etiological classification and clinical classification, and the latter is the most practical.

Dyslipidemia usually refers to increases in cholesterol, TG, or both levels in serum. This condition is generally called hyperlipidemia. In fact, dyslipidemia also extensively refers to various blood lipid abnormalities, including HDL-C hypolipidemia. The classification is complicated. The simplest classifications include the etiological classification and clinical classification, and the latter is the most practical.[16,23,24]

5.1 Etiological classification of dyslipidemia

5.1.1 Secondary hyperlipidemia

Secondary hyperlipidemia refers to dyslipidemia caused by other diseases. The diseases that can induce dyslipidemia primarily include obesity, diabetes, nephrotic syndrome, hypothyroidism, renal failure, liver disease, systemic lupus erythematosus, glycogen storage disease, myeloma, lipoatrophy, acute porphyria, and polycystic ovary syndrome. In addition, some drugs such as diuretics, non-cardiac selective β-blockers, and glucocorticoids can also induce secondary dyslipidemia.

5.1.2 Primary hyperlipidemia

In addition to the association between unhealthy lifestyles (e.g., high energy, high fat, and high sugar diet; excessive drinking; and others) and dyslipidemia, most cases of primary hyperlipidemia are caused by mutations on a single gene or multiple genes. Because hyperlipidemia caused by gene mutations has a family aggregation feature and an obvious genetic tendency (especially in people with a single gene mutation), this condition is usually called familial hyperlipidemia in the clinic.

For example, loss-of-function mutations on the gene encoding the LDL-C receptor, mutations on the gene encoding the Apo B that interacts with the LDL-C receptor, gain-offunction mutations on the gene encoding proprotein convertases subtilisin/kexin type 9 (PCSK9) that degrades the LDL-C receptor, and mutations on the gene encoding the LDL-C receptor modulator that modulates the LDL-C receptor to the surface of the plasma cell membrane can cause familial hypercholesterolemia (FH). In more than 80% of patients, FH is caused by a single gene mutation; however, hypercholesterolemia is associated with multiple gene mutations. Loss-of-function mutations on the LDL-C receptor gene are the major cause of FH. The incidence of homozygous familial hypercholesterolemia (HoFH) is approximately 1/300,000-1/160,000, whereas the incidence of heterozygous familial hypercholesterolemia (HeFH) is approximately 1/500-1/200.

Familial hypertriglyceridemia is caused by a single gene mutation. This condition is usually caused by a gene mutation to the lipoprotein lipases that are involved in TG metabolism, on the Apo C2 gene, or on the Apo A5 gene. It presents as severe hypertriglyceridemia (TG >10 mmol/L), and the incidence rate is 1/1000,000. Mild and moderate hypertriglyceridemia are usually associated with multiple gene mutations.[25,26]

5.2 Clinical classification of dyslipidemia

In practice, dyslipidemia can be stratified based on a simple clinical classification (Table 12).

Table 12 Clinical Classification of Dyslipidemia

Type	TC	TG	HDL-C	Equal to WHO phenotype
Hypercholesterolemia	Increase			IIa
Hypertriglyceridemia		Increase		IV, I
Mixed hyperlipidemia	Increase	Increase		IIb, III, IV, V
HDL-C hypolipidemia			Decrease	

LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; WHO: world health organization.

6 Dyslipidemia screening

Highlights: Regular blood lipid examinations are an important measure for managing blood lipid levels and cardiovascular disease.

The early detection of individuals with dyslipidemia and the monitoring of their blood lipid level changes are important for the effective implementation of management measures for ASCVD. All MAST institutions in China have the ability to determine blood lipid levels. The detection and monitoring work for patients with dyslipidemia is primarily implemented through routine blood lipid examination in the populations who visit medical institutions. These populations include those who already have ASCVD as well as those who have not developed ASCVD. Health examinations are also an important route to detect dyslipidemia. For the early detection of dyslipidemia, adults between 20-40 years old should receive at least one blood lipid measurement (including TC, LDL-C, HDL-C, and TG) every 5 years. Men older than 40 years of age and postmenopausal women should receive blood lipid measurements every year. Patients with ASCVD and high-risk populations should receive one blood lipid measurement every 36 months. Patients who are admitted into hospitals because of ASCVD should receive blood lipid measurements at admission or within 24 h of admission.

The key participants for blood lipid examination are (1) people with a history of ASCVD; (2) populations with multiple ASCVD risk factors (e.g., hypertension, diabetes, obesity, and smoking); (3) people with a family history of early-onset cardiovascular diseases (i.e., immediate male family members younger than 55 years old or immediate female family members younger than 65 years old who develop ischemic cardiovascular disease) or patients with familial hyperlipidemia; and (4) people with skin or tendon xanthomas and Achilles tendon thickening. Many factors influence blood lipid detection results. Implementing blood lipid detection should work according to the requirements of the clinical recommendations for determining blood lipids (Supplement 1).

7 Overall cardiovascular risk assessment

Highlights: Using different intensities of intervention measures based on the risk of developing ASCVD is the core strategy for the management of dyslipidemia. Overall cardiovascular risk assessment is the basis of dyslipidemia treatment decisions. Overall cardiovascular risk assessment should be performed according to recommended procedures. For people younger than 55 years old, a lifetime risk for cardiovascular disease should be considered.

LDL-C or TC levels are independent predictors of the risk of developing ASCVD in individuals and populations.[27–29] However, the risk levels of developing ASCVD in individuals are determined not only by the level of cholesterol but also by the number and levels of comorbid risk factors of ASCVD.[29–31] Individuals with the same LDL-C level might have significantly different overall risks regarding the development of ASCVD because of the different numbers and levels of other risk factors. More importantly, the overall ASCVD risk is not simply an addition of the cholesterol level and the independent functions of other risk factors; rather, it is the result of the complicated interaction between the cholesterol level and many combined risk factors. Therefore, the same cholesterol level can cause greater harm because of the presence of other risk factors. The comprehensive assessment of the overall risk of ASCVD is a necessary prerequisite for the management of dyslipidemia. The assessment of the overall risk of ASCVD can not only help to confirm the decision of lipid-lowering treatment for patients dyslipidemia but also help clinical physicians make personalized comprehensive treatment decisions targeting multiple risk factors, thereby reducing the overall risk of ASCVD in patients to the greatest degree. Currently, the core content of the dyslipidemia management guidelines released by China and other countries include the assessment methods and risk stratification standards for the overall risk of developing ASCVD.[9,12,13,16,22,32–35] The 2007 blood lipid guidelines proposed using the risk of development of "ischemic cardiovascular disease" (i.e., coronary heart disease and ischemic stroke) to reflect the comprehensive pathogenic risk of the major risk factors of dyslipidemia and other cardiovascular diseases. For people at moderate risk of developing ASCVD in 10 years who are < 55 years old, this edition of the "Guidelines" add recommendations for the assessment of the lifetime risk of ASCVD for the early recognition of individuals with a high lifetime risk of ASCVD to perform active interventions.[10]

During risk assessment, people who have been diagnosed with ASCVD are directly listed as a high-risk population. People who meet one of the following conditions are directly listed as a high-risk population: (1) LDL-C ≥ 4.9 mmol/L (190 mg/dL); (2) 1.8 mmol/L (70 mg/dL) ≤ LDL-C <4.9 mmol/L (190 mg/dL), and diabetes patients older than 40 years of age. The very high-risk and high-risk populations who meet the above conditions do not need to receive an ASCVD risk stratification based on their number of risk factors.

When considering whether a lipid-lowering treatment is required, individuals who do not meet the above three conditions should receive an assessment of the overall risk of developing ASCVD over the following 10 years according to the procedures shown in Figure 1. The risk assessment revised in the "Guidelines" has 21 combinations according to the level of LDL-C or TC, the presence of hypertension, and the number of other ASCVD risk factors. In addition, according to the average 10-year incidence risk of ASCVD across different

combinations, these levels are defined as low-risk, medium-risk, and high-risk: < 5%, 5%-9%, and ≥ 10%, respectively. This revision continues the risk-stratification program published in the 2007 Blood Lipid Guidelines to use hypertension as an important parameter in risk stratification (Figure 3). This version of the "Guidelines" provides a more quantitative color figure of the risk stratification of ASCVD development as the reference for risk stratification (Supplement 2).

People who meet any of the following conditions can be directly listed as a high-risk or very high-risk population

Very high-risk: ASCVD patients

High-risk: (1) LDL-C ≥ 4.9 mmoml/L or TC ≥ 7.2 mmol/L

(2) Diabetes patients [LDL-C: 1.8–4.9 mmol/L (or TC: 3.1–7.2 mmol/L) and age ≥ 40 years]

People who do not meet the conditions, assessment of 10-year incidence risk of ASCVD

*Risk factor	Stratification of serum cholesterol levels (mmol/L)		
	3.1≤ TC ≤ 4.1 or 1.8 ≤ LDL-C < 2.6	4.1 ≤ TC ≤ 5.1 or 2.6 ≤ LDL-C < 3.4	5.2 ≤ TC < 7.2 or 3.4 ≤ LDL-C < 4.9
Without hypertension 0–1	Low-risk (< 5%)	Low-risk (< 5%)	Low-risk (< 5%)
2	Low-risk (< 5%)	Low-risk (< 5%)	Medium-risk (5%–9%)
3	Low-risk (< 5%)	Medium-risk (5%–9%)	Medium-risk (5%–9%)
With hypertension 0	Low-risk (< 5%)	Low-risk (< 5%)	Low-risk (< 5%)
1	Low-risk (< 5%)	Medium-risk	Medium-risk (5%–9%)
2	Medium-risk (5%–9%)	High-risk (≥ 10%)	High-risk (≥ 10%)
3	High-risk (≥ 10%)	High-risk (≥ 10%)	High-risk (≥ 10%)

For people with medium 10-year incidence risk of ASCVD and age < 55 years, assessment of lifetime risk

People with any two or more items of the above risk factors are defined as a high-risk ASCVD population

- Systolic pressure ≥ 160 mmHg or diastolic pressure ≥ 100 mmHg
- Non-HDL-C ≥ 5.2 mmol/L (200 mg/dL)
- HDL-C < 1.0 mmol/L (40 mg/dL)
- BMI ≥ 28 kg/m^2
- Smoking

*Including smoking, low HDL-C, and men ≥ 45 years of age or women ≥ 55 years of age. The risk assessment and treatment of patients with chronic kidney disease refer to the treatment of dyslipidemia in special populations.

ASCVD: atherosclerotic cardiovascular disease; BMI: body mass index; CM: chylomicron; HDL-C: high-density lipoprotein cholesterol; IDL: intermediate-density lipoprotein; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; VLDL:very-low-density lipoprotein cholesterol.

Figure 3 The Risk Assessment Flow Chart of ASCVD

Because studies in China and other countries have already discovered the effect of the risk factor levels on the lifetime risk of people younger than 55 years old,[10,31,36,37] this revision of the "Guidelines" recommends assessing the lifetime risk of ASCVD in people who have medium 10-year incidence risk for ASCVD to identify middle-aged and young individuals who have high lifetime risks for developing ASCVD in 10 years to perform early interventions on certain risk factors including blood lipids. If people with medium 10-year incidence risk of ASCVD have any two or more of the following risk factors, then their lifetime risk of ASCVD is high: (1) systolic pressure ≥160 mmHg or diastolic pressure ≥100 mmHg; (2) non-HDL-C ≥5.2 mmol/L (200 mg/dL); (3) HDL-C <1.0 mmol/L (40 mg/dL); (4) body mass index (BMI) ≥28 kg/m^2; and (5) smoking.

8 Principles of dyslipidemia treatment

Highlights: Very high-risk, LDL-C <1.8 mmol/L; high-risk, LDL-C <2.6 mmol/L; medium-risk and low-risk, LDL-C <3.4 mmol/L.

People who cannot achieve the target value because the baseline value of LDL-C is higher should reduce LDL-C values by at least 50%. Very-high-risk people who have LDL-C baseline values within the target still should reduce LDL-C levels by approximately 30%.

For clinical lipid-lowering goal attainment, statin lipid-lowering drugs are preferred. At the beginning of treatment, medium-intensity statins should be applied. Doses should be properly adjusted according to individual lipid-lowering efficacy and tolerance conditions. If the cholesterol level cannot reach the goal, then other lipid-lowering drugs can be used in combination.

Dyslipidemia treatment seeks to manage ASCVD and reduce the incidence risk of clinical cardiovascular events, such as myocardial infarction, and ischemic strike, and coronary heart disease mortality. Because of the differences in genetic background and living environments, the risk levels of the development of ASCVD among individuals significantly differ. Lipid-lowering treatment can benefit patients with ASCVD and high-risk populations. Whether the lipid-lowering drug treatment should be initiated should be based on the risk levels of ASCVD in individuals in the clinic (Class I recommendation, Level A evidence).

8.1 Lipid-lowering treatment targets

Dyslipidemia, especially an increase in LDL-C, is the key factor that causes the initiation and progression of ASCVD. Many clinical studies have repeatedly confirmed that regardless of the drugs or measures adopted, as long as the serum LDL-C level can be reduced, atherosclerotic lesions can be stably delayed or regressed, and the incidence, morbidity, and mortality of ASCVD can be significantly reduced. All of the guidelines for the management of dyslipidemia in China and other countries emphasize that LDL-C plays a core role in developing ASCVD, and they advocate reducing serum LDL-C levels to manage ASCVD risk.[9,12,35,38] Therefore, the use of LDL-C as the preferred intervention target is recommended (Class I recommendation, Level A evidence).

Non-HDL-C can be used as the secondary intervention target (Class IIa recommendation, Level B evidence). Given that patients with hypertriglyceridemia have increased remnant lipoproteins in their bodies that might cause atherosclerosis, non-HDL-C is used as the secondary intervention target.

8.2 Setting up lipid-lowering target values

Clinical physicians are familiar with establishing target values of lipid-lowering treatments and have experience applying such measures. However, certain newly published dyslipidemia diagnoses and treatment guidelines in other countries do not recommend establishing lipid-lowering target values,[12,35] because no evidence from randomized controlled studies support the specific target values of blood lipid treatment, and it is not known what type of blood lipid target values engender the largest degree of reduction of the risks of ASCVD. However, if lipid-lowering target values are eliminated, then the compliance of patients who take lipid-lowering drugs will be severely affected. Regarding the benefits of lipid-lowering treatment, a long-term adherence to treatment is important. Only when lipid-lowering target values are established can physicians more accurately evaluate the effectiveness of treatment methods, effectively communicate with patients, and increase the compliance of patients regarding lipid-lowering drugs. Furthermore, no evidence or reasons exists to eliminate lipid-lowering target values in China.[38,39] Therefore, target values should be established in a lipid-lowering treatment (Class I recommendation, Level C evidence).

8.3 Lipid-lowering goal attainment values

The basic target value of cholesterol to be achieved in lipid-lowering treatment should be confirmed according to the different risk levels of ASCVD. The recommendation for the reduction of LDL-C to a certain cutoff point (i.e., target value) is primarily based on risk-benefit analysis; when the risk for developing a cardiovascular event in the future is high, the benefit is larger. Although LDL-C might be reduced to a lower level, more clinical cardiovascular benefits exist, and the drug-related adverse reactions will also significantly increase. In addition, health economics are also important factors that affect making treatment decisions and should be considered.

Patients who are diagnosed with ASCVD [including acute coronary syndrome (ACS)], stable coronary heart disease, post revascularization, ischemic cardiomyopathy, ischemic stroke, transient ischemic attack (TIA), and peripheral atherosclerosis in the clinic all belong to the very high-risk population.[13,35] In the non-ASCVD population, risk assessment is performed according to cholesterol level, its severity, and the number of risk factors. These patients are divided into high-risk, medium-risk, and low-risk groups. The target value for reducing LDL-C is determined based on the risk of developing ASCVD among individuals. The LDL-C and non-HDL-C target values that must be achieved by populations with different risks show large differences (Table 13, Class I recommendation, Level B evidence).

Table 13 The Goal Attainment Values of LDL-C and non-HDL-C Treatments Across Different ASCVD Risk Populations [mmol/L (mg/dL)]

Risk level	LDL-C	Non-HDL-C
Low/medium risk	< 3.4 (130)	< 4.1 (160)
High risk	< 2.6 (100)	< 3.4 (130)
Very high risk	< 1.8 (70)	< 2.6 (100)

HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

All clinical study results of enhanced statin therapy show that several increased doses of statins can reduce the risk of developing ASCVD events; however, the absolute values of these benefits are small, and the all-cause mortality is not decreased.[40] Studies of statins combined with ezetimibe treatment have also obtained similar results.[41] Reduction of LDL-C from 1.8 mmol/L to 1.4 mmol/L can further reduce the absolute risk of cardiovascular events by 2% and the relative risk by 6.4%; however, the risks of cardiovascular mortality and all-cause mortality are not reduced. These results suggest that although a clinical benefit exists after LDL-C is reduced, the absolute benefits are already decreased.

If the baseline value of LDL-C is high, then LDL-C is difficult to reduce to the basic target value after treatment with the existing standard lipid-lowering treatment for 3 months. Thus, the alternative goal of at least 50% reduction of LDL-C should be considered (Class IIa recommendation, Level B evidence). In the clinic, the LDL-C baseline values of certain very-high-risk patients are already within the basic target values. At this time, LDL-C can be reduced by approximately 30% from the baseline value (Class I recommendation, Level A evidence).

The target value of non-HDL-C is higher than that of LDL-C by 0.8 mmol/L (30 mg/dl). The target values of non-HDL-C treatment in populations at different risks are shown in Table 13 (Class I recommendation, Level B evidence).

8.4 Lipid-lowering goal attainment strategy

Over the last 20 years, the results of many large-scale clinical trials consistently show that statins can significantly reduce the risk of cardiovascular events (including myocardial infarction, coronary heart disease mortality, ischemic stroke, and others) with regard to the primary and secondary prevention of ASCVD. Statins have already become the most important drugs in the management of this group of diseases. Therefore, to lower lipids, statins should be a first-line treatment chosen in clinical practice (Class I recommendation, Level A evidence).

However, how to reasonably and effectively use statins remains controversial. Recent guidelines in other countries recommend using high-intensity (equivalent to the maximum maximum allowable dose) statins at the beginning of clinical practice. However, the increased benefits and safety of the maximum allowable dose of statins in the Chinese population have not been confirmed.[42] The HPS2-THRIVE study indicates that the Chinese population can achieve lower LDL-C levels than their European counterparts when the exact

same statin drug and dose are used.[43] The DYSISCHINA study showed that an increase of statin doses does not increase the goal attainment rate of LDL-C.[44] The CHILLAS study did not show that Chinese patients with ACS obtain more benefits from high-intensity statins.[45] In the Chinese population, safety must be considered during the use of high-intensity statins. More studies have indicated that high-intensity statin therapy is accompanied by high risks of myopathy and increases in the liver enzymes that are more prominent in the Chinese population. The HPS2-THRIVE study indicated that the incidence of adverse liver reactions was significantly higher in Chinese patients than in European patients during treatment with medium-intensity statins. The rate of increase in liver enzymes (> 3 times of the upper limit of the normal value) was more than 10 times higher than that among European patients, and the risk of myopathy was also 10 times higher. Currently, no safety data exist regarding high-intensity statin therapy in the Chinese population.

One feature of the efficacy of lipid-lowering statin drugs is that the initial dose of every statin has excellent lipidlowering efficacy. When the dose is doubled, LDL-C is further reduced by 6% (the statin efficacy "rule of six"). When the statin dose is doubled, the drug cost proportionally increases, whereas the increase of the efficacy for LDL-C reduction is relative small. Therefore, the use of medium-intensity statins is recommended for initial treatment. The dose is properly adjusted according to individual lipid-lowering efficacy and tolerance conditions. If the cholesterol level does not reach the target, then other lipidlowering drugs (e.g., ezetimibe) can be used in combination to obtain safe and effective lipid-lowering effects (Class I recommendation, Level B evidence).

8.5 Other dyslipidemia interventions

In addition to active cholesterol interventions, whether other dyslipidemia conditions also require treatment lacks the evidence of relevant clinical trial benefits. The appropriate level of serum TG is < 1.7 mmol/L (150 mg/dL). When serum TG is ≥ 1.7 mmol/L (150 mg/dL), non-drug intervention measurement is first applied including therapeutic diet, reduction of body weight, and abstinence from alcohol. If the TG level only shows a mild-to-moderate increase [i.e., 2.3-5.6 mmol/L (200-500 mg/dL)] to manage the risk of ASCVD, then although the reduction of the LDL-C level is the major goal, non-HDL-C should also reach the target value. If non-HDL-C cannot reach the target value even after statin therapy, then fibrates and high purity fish oil preparations should be used additionally with statins. For patients with severe hypertriglyceridemia and fasting TG levels of ≥ 5.7 mmol/L (500 mg/dL), drugs that reduce TG and VLDL-C should be considered first (e.g., fibrates, high purity fish oil preparations, or niacin).

For people with HDL-C < 1.0 mmol/L (40 mg/dL), diet should be controlled and lifestyle should be improved. Currently, not enough evidence exists for drug interventions.

8.6 Lifestyle interventions

Diet and lifestyle typically and significantly influence dyslipidemia. Dietary treatment and lifestyle improvements are the basic measures of dyslipidemia treatment. Whether a drug lipid-lowering therapy is performed, diet control and lifestyle improvement must be assured (Class I recommendation, Level A evidence). Excellent lifestyle habits include adhering to a

heart-healthy diet and regular exercise, avoiding tobacco, and maintaining an ideal body weight. Lifestyle intervention is the therapeutic measure with the best cost-benefit and risk-benefit ratios.

For low- and medium-risk patients, if LDL-C fails to reach the goal after 6 months of lifestyle intervention, then a low/medium intensity statin therapy is initiated. For highand very-high-risk patients, a medium-intensity statin drug treatment is initiated immediately combined with a lifestyle intervention.

8.7 Treatment process monitoring

Patients with dietary and non-drug treatment should test their blood lipid levels again in the first 3-6 months. If blood lipid control reaches the recommended target, then the non-drug treatment should continue and re-examinations should be performed every 6 months to 1 year. People who have attained long-term goals should receive a re-examination once every year. People who take lipid-lowering drugs require closer blood-lipid monitoring. People who take lipidlowering drugs for the first time should receive re-examinations for blood lipids, transaminases, and creatine kinase within 6 weeks of drug administration. If their blood lipids reach the target value and no adverse drug reaction exists, then re-examination should be gradually changed to once every 6-12 months. If blood lipid levels do not reach the goal and no adverse drug reaction occurs, then monitoring should be performed once every 3 months. If blood lipids do not reach the target value even after 3-6 months of treatment, the dose and type of lipid-lowering drugs should be adjusted, or the treatment should be combined with lipidlowering drugs with different action mechanisms. After each adjustment of the type or dose of lipid-lowering drugs, re-examination should be performed within 6 weeks of treatment. Therapeutic lifestyle change (TLC) and lipidlowering drug treatment must be continued over the long term to obtain excellent clinical benefits.

9 Therapeutic lifestyle changes

Highlights: Total energy is controlled by fulfilling the requirement of daily essential nutrition. The percentage of composition of all nutritional elements should be selected reasonably. People should control body weight, quit smoking, limit drinking, and adhere to regular medium-intensity metabolic exercise.

Dyslipidemia is closely associated with diet and lifestyle. Dietary therapy and lifestyle improvement are the basic measures of dyslipidemia treatment.[46] Whether the lipidlowering drug treatment is chosen, control of diet and improvement of lifestyle should be maintained (Table 14). Daily essential nutrition and total energy requirements should be met when the total amount of saturated fatty acid and trans-fat uptake exceeds the upper limit; these compounds should be replaced with unsaturated fatty acids. The recommended daily cholesterol intake is <300 mg; lipid intake should not be >20%-30% total energy, especially for high-risk people for ASCVD and other similar conditions. Saturated fatty acid intake should be <10% total energy for the general population. For patients with hypercholesterolemia, the amount of saturated fatty acid intake should be <7% total energy, and the amount of trans-fat intake should be <1% total energy. Patients with hypertriglyceridemia should reduce their total amount of daily fat intake as low as possible,

and their daily consumption of cooking oil should be < 30 g. Regarding lipid intake, food that is rich in omega-3 polyunsaturated fatty acids should be selected first (e.g., deep-sea fish, fish oil, and vegetable oil).

Table 14 Basic Lifestyle Change Elements

Element	Recommendation
Limiting dietary ingredients that can increase LDL-C	
Saturated fatty acid	< 7% of total energy
Dietary cholesterol	< 300 mg/dL
Increasing dietary ingredients to reduce LDL-C	
Plant sterols	2-3 g/dL
Water soluble dietary fiber	10-25 g/dL
Total energy	Adjusting to the level that can maintain ideal body weight or reduce body weight
Physical activity	Maintaining medium-intensity exercise and consuming at least 200 kcal

LDL-C: low-density lipoprotein cholesterol.

The recommended daily carbohydrate intake accounts for 50%-65% of total energy. Carbohydrates rich in dietary fibers and low in glycemic index should be chosen to replace saturated fatty acids. Daily diets should include 25-40 g of dietary fiber (7-13 g of water-soluble dietary fiber). The carbohydrate intake should be primarily cereals, tubers, and whole grains. The intake of added sugar should not be over 10% total energy (this percentage is lower for people with obesity or hypertriglyceridemia). Food additives such as plant sterols/alkanols (2-3 g/dL) and soluble/viscous dietary fibers (10-25 g/dL) can help with blood lipid control; however, their safety requires long-term monitoring.

9.1 Controlling body weight

Obesity is an important risk factor for dyslipidemia. Overweight or obese people with dyslipidemia should uptake less energy than the body energy consumed to gradually reduce body weight to the ideal status. Reducing the total energy from daily food (by 300-500 kcal daily), improving dietary structure, and increasing physical activity can reduce more than 10% body weight in overweight and obese people. The maintenance of a health body weight (BMI: 20.0-23.9 kg/m^2) is conducive to blood lipid control.

9.2 Physical activity

Medium-intensity metabolic exercise is recommended for 5–7 days every week, 30 min each time. Patients with ASCVD should first perform an exercise load test; after the safety of this exercise has been fully evaluated, physical activity is then performed.

9.3 Quit smoking

Patients should completely quit smoking and effectively avoid the inhalation of secondhand smoke to prevent ASCVD and to increase HDL-C levels. Smoking cessation treatments, smoking cessation hotline consultation, and medicines can be used to help quit smoking.

9.4 Limit drinking

A moderate amount of drinking (20-30 g of alcohol daily for men and 10-20 g of alcohol daily for women) can increase HDL-C levels. Even a small amount of drinking can further increase TG levels in patients with hypertriglyceridemia. No exact evidence exists regarding the influence of drinking on cardiovascular events. Restricted drinking is advocated.

10 Lipid-lowering drug treatments

Highlights: Whether the lipid-lowering drug treatment should be initiated should be based on the risk levels of ASCVD in individuals in the clinic.

The reduction of LDL-C levels should be used as the preferred intervention target in the management of ASCVD risks. Non-HDL-C can be used as the secondary intervention target.

Lipid-lowering treatment should establish very high-risk, LDL-C < 1.8 mmol/L; high-risk, LDL-C < 2.6 mmol/L; medium-risk and low-risk, LDL-C < 3.4 mmol/L.

People who cannot achieve the target value because the baseline value of LDL-C is higher should reduce LDL-C values by at least 50%. Very-high-risk people who have LDL-C baseline values within the target still should reduce LDL-C levels by approximately 30%.

For clinical lipid-lowering goal attainment, statin lipid-lowering drugs are preferred. At the beginning of treatment, medium-intensity statins should be applied. Doses should be properly adjusted according to individual lipid-lowering efficacy and tolerance conditions. If the cholesterol level cannot reach the goal, then other lipid-lowering drugs can be used in combination.

The blood lipid metabolic pathway in the human body is complicated. Many enzymes, receptors, and transport proteins are involved. Many types of lipid-lowering drugs can be chosen in clinical practice. Generally, these drugs can be divided into two large groups: (1) drugs that primarily reduce cholesterol; and (2) drugs that primarily reduce TG. Some lipid-lowering drugs can reduce both cholesterol and TG. Severe hyperlipidemia usually requires the combined application of many lipid-lowering drugs to obtain excellent efficacy.

10.1 Drugs that primarily reduce cholesterol

The major action mechanisms of this group of drugs inhibit cholesterol synthesis in hepatocytes, accelerate LDL-C catabolism, or reduce cholesterol absorption in the intestinal tract. This group of drugs includes statins, cholesterol absorption inhibitors, probucol, bile acid sequestrants, and other lipid-lowering drugs (e.g., Zhibitai and policosanol).

10.1.1 Statins

Statins, also known as 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, can inhibit the rate-limiting enzyme of cholesterol synthesis (HMG-CoA reductase) to reduce cholesterol synthesis and further upregulate the LDL-C receptor on the cell surface and accelerate serum LDL-C catabolism. In addition, statins can also inhibit

VLDL synthesis. Therefore, statins can significantly reduce serum TC, LDL-C, and Apo B levels as well as reduce serum TG levels and mildly increase HDL-C levels.

The advent of statins was a milestone in the history of human ASCVD management. The 4S clinical trial first confirmed that statins reduce coronary heart disease mortality and overall patient mortality.[47] The subsequent CARE,[48] LIPID,[49] and LIPS[50] studies also confirmed the important functions of this group of drugs with regard to the secondary prevention of coronary heart disease. The HPS study indicated that statin therapy benefits the high-risk population when their baseline cholesterol is not high.[51] The clinical trials regarding enhanced statin therapy primarily included PROVE-IT,[52] A to Z,[53] TNT,[54] MIRACL,[55] and IDEAL.[56] Compared with the routine dose of statins, enhanced statin therapy for patients with coronary heart disease further reduces the likelihood of cardiovascular events;[52,54] however, the reduction level is not high,[53,56] and total mortality is not reduced.[57] The ASTEROID study confirmed that statin therapy reverses coronary atherosclerosis.[58] The WOSCOPS,[59] AFCAPS/TexCAPS,[60] CARDS,[61] JUPITER,[62] and HPS[51] studies expanded the application of statins from patients with ASCVD to primary prevention and more extensive populations. Currently, the function of statins with regard to the primary prevention of cardiovascular disease among high-risk populations has been affirmed. However, the application effect in people at low risk of cardiovascular disease awaits further study. Many studies have targeted special populations for investigation. The SPARCL,[63] PROSPER,[64] CARDS,[61] ALLHAT-LLT,[65] and ASCOT-LLA[66] studies individually showed that statins have clinical benefits in the elderly as well as patients with stroke, diabetes, or hypertension. Furthermore, evidence from Chinese clinical studies does not support the cardiovascular benefits of shortterm enhanced statin therapy before percutaneous coronary intervention (PCI) among patients with ACS. Moreover, the newest guidelines in other countries do not recommend short-term enhanced statin intervention strategies during the perioperative period of PCI.

Statins are applicable for patients with hypercholesterolemia, mixed hyperlipidemia, or ASCVD. Currently, lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, rosuvastatin, and pitavastatin are used in clinical practice in China. The cholesterol reduction levels have large differences depending on the different types and doses of statins. However, when any statin does is doubled, the continued reduction of LDL-C is only 6% (i.e., the so-called “rule of six of statin efficacy”). Statins can reduce TG levels by 7%-30% and increase HDL-C levels by 5%-15%.

Statins can be administered once per day at any time. However, the administration of LDL-C at night might be associated with higher levels of LDL-C reduction. After the expected efficacy of statin administration is obtained, the long-term administration should be continued. If patients can tolerate this treatment, then drug withdrawal should be avoided. Previous studies have suggested that statin withdrawal might increase the development of cardiovascular events.[67] If adverse reactions occur after statin administration,then this treatment should be replaced with another type of statin, the dose should be reduced, and drug administration should be performed every other day;[68] otherwise, other non-statin lipid lowering drugs should be used.

The analytic results of the Cholesterol Treatment Trials' (CTT) collaboration indicate that when LDL-C is reduced by 1 mmol/L after statin therapy in populations with different cardiovascular risk stratifications, the relative risk of major cardiovascular events is reduced by 20%, and allcause mortality is reduced by 10%, whereas the mortality caused by non-cardiovascular reasons does not increase.[57,69] Current studies have repeatedly confirmed that the level of clinical reduction benefits of ASCVD by statins is linearly and positively correlated with the level of LDL-C reduction. The clinical benefits produced by statin therapy originate from the effect of LDL-C reduction. The levels of LDL-C reduction via different types and doses of statins are shown in Table 15.[35]

Table 15 The Cholesterol Reduction Intensity of Stains

High intensity (daily dose can reduce LDL-C by ≥ 50%)	**Medium intensity (daily dose can reduce LDL-C by 25%-50%)**
Atorvastatin 40-80 mg*	Atorvastatin 10-20 mg
Rosuvastatin 20 mg	Rosuvastatin 5-10 mg
	Fluvastatin 80 mg
	Lovastatin 40 mg
	Pitavastatin 2-4 mg
	Pravastatin 40 mg
	Simvastatin 20-40 mg
	Xuezhikang 1.2 g

*Studies of atorvastatin (80 mg) among the Chinese population are limited; please use with caution. LDL-C: low-density lipoprotein cholesterol.

Although Xuezhikang capsules are classified as a lipidlowering Chinese medicine, their lipid-lowering mechanism is similar to that of statins. These capsules are refined via the biological fermentation of a special monascus added to rice using the modern GMP standard manufacturing process. The main ingredients of these capsules include 13 types of natural statin compounds, including lovastatin without a crystal structure and its homologs. The commonly used dose is 0.6 g twice per day. The China Coronary Secondary Prevention Study (CCSPS) and other clinical studies confirmed that Xuezhikang capsules reduce cholesterol and significantly reduce the overall mortality of patients with coronary heart disease, the incidence of cardiovascular events, and number of side effects.[70-73]

Most people show excellent tolerance to statins. Adverse reactions are primarily observed in patients who receive large doses of statin therapy. The most common manifestations are discussed below.

(1) Abnormal liver function.[74,75] The main presentation of this condition is the increase of transaminases. The incidence is approximately 0.5%-3%, and it shows dose dependence. Patients with an increase of serum alanine aminotransferase (A), aspartate aminotransferase (AST) higher than three times the upper limit of normal values, and the combined increase of total bilirubin should reduce or discontinue drug use. Patients with an increase of transaminases within three times of the upper limit of normal values can be observed based on the original doses or reduced doses. Some patients can restore normal transaminases after

this treatment. The application contraindications of statins are decompensated cirrhosis and acute liver failure.

(2) Statin-related adverse muscle reactions include myalgia, myositis, and rhabdomyolysis.[76,77] When patients have muscle discomfort, weakness, or both and continuous creatine kinase detection shows progressive increases, statins doses should be reduced or the drugs should be discontinued.

(3) The long-term administration of statins might increase the risk of new-onset diabetes.[78] The incidence is approximately 10%-12%, and it is classified as a statin effect. The overall benefits of statins on cardiovascular diseases are more significant than the risk of new-onset diabetes. Patients with diabetes or those at high risk for diabetes who have statin therapy indications should adhere to the administration of this group of drugs.

(4) Statin therapy can cause cognitive dysfunction.[79] However, this dysfunction is transient, and its incidence is not high. The results of a meta-analysis showed that statins do not have adverse effects on renal function.[80] The adverse reactions of statins also include headache, insomnia, and depression as well as digestive tract symptoms such as indigestion, diarrhea, abdominal pain, and nausea.

10.1.2 Cholesterol absorption inhibitors

Ezetimibe can effectively inhibit cholesterol absorption in the intestinal tract. The IMPROVE-IT study indicated that the administration of ezetimibe based on simvastatin further reduces the likelihood of cardiovascular events in patients with ACS.[41] The SHARP study showed that a combined treatment with ezetimibe and simvastatin improves cardiovascular disease prognosis in patients with CKD[81]. The recommended dose of ezetimibe is 10 mg/d. This drug shows excellent safety and tolerance, and the adverse reactions are mild and mostly transient. The major presentations are headache and digestive tract symptoms.

When combined with statins, ezetimibe can produce adverse reactions such as transaminase increases and myalgia. Ezetimibe is prohibited during pregnancy and lactation.

10.1.3 Probucol

Probucol influences lipoprotein metabolism through an incorporation into the core of LDL-C particles; thus, LDL-C is easily cleared through the non-receptor pathway. The commonly used dose of probucol is 0.5 g twice per day. This drug is primarily applicable for patients with hyperlipidemia, especially those with HoFH or xanthoma. Probucol relieves skin xanthomas.[82,83] Its common adverse reactions are gastrointestinal in nature. Probucol can also induce dizziness, headache, insomnia, and skin rash. Rare but severe adverse reactions include QT interval prolongation. Probucol is prohibited for patients with ventricular arrhythmia, QT interval prolongation, or hypokalemia.

10.1.4 Bile acid sequestrants

Bile acid sequestrants are basic anion exchange resins. They can block the reabsorption of cholesterol in the bile acid in the intestinal tract.[84] The clinical dosage of cholestyramine is 5 g three times per day, 5 g of colestipol three times per day, and 1.875 g of colesevelam twice per day. When combined with statins, these drugs can significantly increase lipid-lowering efficacy. The most common adverse reactions include gastrointestinal discomfort and constipation; furthermore, they can influence the absorption of certain drugs. The absolute contraindications of this group of drugs are abnormal dysbetalipoproteinemia and serum TG >4.5 mmol/L (400 mg/day).

10.1.5 Other lipid-lowering drugs

Zhibitai is a compound preparation of monascus and traditional Chinese medicine (i.e., hawthorn, alisma, and atractylodes). The most commonly used dose is 0.24-0.48 g twice per day. This compound has mild-to-moderate cholesterol-reducing functions.[85,86] This drug has few adverse reactions.

Policosanol is a mixture containing 8 types of advanced aliphatic alcohol purified from sugarcane wax. The most commonly used dose is 10-20 mg/day. Its lipid-lowering effect is slow, and rare but adverse reactions are known.[87,88]

10.2 Major TG-lowering drugs

Three major TG-lowering drugs exist: fibrates, niacin, and high-purity fish oil preparations.

10.2.1 Fibrates

Fibrates reduce serum TG levels and increase HDL-C levels through the activation of peroxisome proliferator activated receptor-α (PPARα) and lipoprotein lipase (LPL).[89–93] The most commonly used fibrates include fenofibrate tablets 0.1 g three times per day, micronized fenofibrate 0.2 g once per day, gemfibrozil 0.6 g twice per day, and bezafibrate 0.2 g three times per day. The most common adverse reactions are similar to those of statins, including liver, muscle, and kidney toxicities. The incidence rates of increased serum creatine kinase and ALT levels are both < 1%. Meta-analyses of clinical trial results have shown that fibrates can reduce the risk of cardiovascular events in people with high TG combined with low HDL-C by approximately 10%. These drugs primarily reduce nonfatal myocardial infarction and coronary revascularization, but they do not significant affect cardiovascular mortality, fatal myocardial infarction, or stroke.[90-92]

10.2.2 Niacin

Niacin, also known as vitamin B3, is an essential vitamin in the human body. Niacin can decrease TC, LDL-C, and TG as well as increase HDL-C in large doses. Its lipid- lowering function is associated with the inhibition of hormone-sensitive lipase activities in adipose tissue, the reduction of free fatty acid entry into the liver, and the decease of VLDL secretion. Niacin has two formulation types: general and sustained-releasing. The sustained-releasing

formulation is more commonly used. The most commonly used dose of sustained-releasing tablets is 1-2 g once per day. Starting with a small dose (0.375-0.5 g/day) before going to bed is recommended. After four weeks, the dose gradually increases to the commonly used maximum dose. The most common adverse reaction is facial flushing. Other reactions include liver damage, hyperuricemia, hyperglycemia, acanthosis, and gastrointestinal discomfort. Niacin is prohibited for patients with chronic active liver disease, active peptic ulcer, or severe gout. The results of a meta-analysis of early clinical trials showed that whether used alone or as a combined application with other lipid-lowering drugs, niacin improves cardiovascular prognosis, reduces the risk of cardiovascular events by 30%, and reduce the risk of coronary events by 25%.[94] Because clinical studies concerning the combination of niacin based on statins suggest that no cardiovascular protective function exists compared with using statins alone,[95,96] niacin is being phased out of the lipid-lowering drug market in many European and American countries.

10.2.3 High-purity fish preparations

The main ingredient of fish oil is n-3 fatty acid (i.e., ω-3 fatty acids). The common dose is 0.5-1.0 g three times per day. Fish oil is primarily used to treat hypertriglyceridemia hypertriglyceridemia.[97–99] Adverse reactions such as digestive tract symptoms are rare, and their incidence is approximately 2%-3%. A few patients have mild increases of transaminases or creatine kinase; a bleeding tendency is sometimes observed. An early clinical study showed that high-purity fish oil preparations reduce the risk of cardiovascular events;[100] however, subsequent clinical trials did not confirm this result.[101,102]

10.3 New types of lipid-lowering drugs

Three new types of lipid-lowering drugs have recently been approved for clinical applications in other countries.

10.3.1 Microsomal triglyceride transfer protein inhibitors

Lomitapide (brand name, Juxtapid) was approved for the market by the US Food and Drug Administration (FDA) in 2012. It is primarily used to treat HoFH. Lomitapide can reduce LDL-C by approximately 40%. This drug has higher adverse reaction rates, and the major presentations are an increase of transaminases or fatty liver.[103,104]

10.3.2 Apolipoprotein B100 synthesis inhibitors

Mipomersen is a second-generation anti-sense oligonucleotide. In 2013, the FDA approved it for use alone or combined with other lipid-lowering drugs to treat HoFH. The action mechanism is an anti-sense oligonucleotide that targets the transcription of Apo B messenger ribonucleic acid (mRNA) to reduce VLDL synthesis and secretion and LDL-C levels. This drug can reduce LDL-C levels by 25%. The most common adverse reaction is an injection site reaction including local rash, swelling, itching, and pain. Most adverse reactions are mild to moderate.[105]

10.3.3 PCSK9 inhibitor

PCSK9 is a secretory serine protease synthesized by the liver that can bind to the LDL-C receptor to cause its degradation, thereby reducing the clearance of serum LDL-C via the LDL-C receptor. Through the inhibition of PCSK9, LDL-C receptor degradation can be blocked to promote LDL-C clearance. Among PCSL09 inhibitors, the development PCSK9 monoclonal antibodies is the most rapid, and additional studies exist on alirocumab, evolocumab, and bococizumab. These study results show that whether used alone or combined with statins, PCSK9 inhibitors significantly reduce serum LDL-C levels and improve other blood lipid indicators including HDL-C and Lp (a). The European Medicines Agency and the US FDA have already approved two injection-type PCKS9 inhibitors (evolocumab and alirocumab) for the market. Preliminary clinical study results indicate that PCSK9 inhibitors can reduce LDL-C and cardiovascular events by 40%-70%.[106,107] Currently, no reports regarding severe or life-threatening adverse effects have been published.[108] This drug is still in the clinical trial stage in China.

10.4 Combined application of lipid-lowering drugs

The combined application of lipid-lowering drugs represents a trend of intervention measures for dyslipidemia. The advantage of a combined application is to increase the goal attainment rate of blood lipid control and simultaneously reduce the incidence of adverse reactions. Statin functions have been recognized; few adverse reactions are known that can reduce overall mortality. The combined lipid-lowering programs are primarily composed of statins and other types of lipid-lowering drugs with different action mechanisms. Different programs exist for the application of drug combinations targeting the different action mechanisms of lipidlowering drugs.

10.4.1 Combined application of statins and ezetimibe

Two types of drugs can individually influence cholesterol synthesis and absorption to produce excellent synergistic effects. Combined treatment can reduce serum LDL-C based on statin therapy by approximately 18%, but it does not increase the adverse reactions of statins.[109–111] Many clinical trials have observed that ezetimibe combined with different types of statins shows excellent lipid-lowering effects.[110,112,113] The IMPROVE-IT and SHARP studies independently showed that the administration of combined statins and ezetimibe in people with high-risk ASCVD and patients with CKD reduces the risk of cardiovascular events.[41,81] People whose cholesterol levels do not reach the target after a medium-intensity statin therapy or who show intolerance should consider medium-to-low intensity statins combined with ezetimibe therapy (Class I recommendation (Level B evidence).

10.4.2 Combined application of statins and fibrates

The combination of these two drugs effectively reduces LDL-C and TG levels, increases HDL-C levels, and reduces sLDL-C. Fibrates include fenofibrate, gemfibrozil, and bezafibrate; of these compounds, fenofibrate has been the most studied and is associated with the most sufficient evidence.[114] Previous studies have suggested that the combined

application of statins and fenofibrate increases cardiovascular benefits among patients with high TG combined with low HDL-C.[115] Fenofibrate is applicable for patients with severe hypertriglyceridemia with or without mixed hyperlipidemia of low HDL-C levels, especially for those with accompanied dyslipidemia, diabetes, and metabolic syndrome and high-risk cardiovascular patients who show poor control of their TG or HDL-C levels after statin therapy. Because the metabolic pathways of statins and fibrates are similar, they both have the possibility of damaging the liver function and risk myositis and myopathy. The chances of an adverse reaction during combined application can increase. Therefore, the safety of the combined application of statins and fibrates should be highly focused. Gemfibrozil combined with statins show relatively higher risks of myopathy. In the beginning of a combined application, small doses should be used via the administration of fibrates in the morning and the administration of statins at night to avoid significant increases in the blood drug concentration. In addition, muscle enzymes and liver enzymes should be monitored closely. If adverse reactions occur, then the dose of statins can be gradually increased.

10.4.3 Combined application of statins and PCSK9 inhibitors

Although PCSK9 inhibitors are still not on the Chinese market, the combined application of statins and PCSK9 inhibitors has already become a method for treating patients with severe dyslipidemia, especially those with FH, in Europe and America. This treatment can cause greater reductions in LDL-C levels and increase goal attainment rates compared with other single drug treatments. Patients with FH, especially those with HoFH, treated with the largest dose of lipid-lowering drugs (e.g., statins+ezetimibe) and lifestyle modification as well as patients with ASCVD and LDL-C levels > 2.6 mmol/L can also use PCSK9 inhibitors, constituting the combined application of three lipid-lowering drugs with different action mechanisms.

10.4.4 Combined application of statins and n-3 fatty acids

The combined application of statins and fish oil preparation n-3 fatty acids can be used to treat mixed hyperlipidemia without increasing adverse reactions. Because taking larger doses of n-3 polyunsaturated fatty acids has a bleeding risk and increases calorie intake in obese patients with diabetes, long-term application is not appropriate. Whether this combination can reduce cardiovascular events is currently under investigation.

11 Other measures for dyslipidemia treatment

Highlights: Lipoprotein-plasma exchange, liver transplantation, partial ileal bypass surgery, and portacaval shunt are used as adjuvant treatment measures for patients with FH. The effect of lipoprotein-plasma exchange has been recognized.

11.1 Lipoprotein-plasma exchange

Lipoprotein-plasma exchange is an important adjuvant treatment measure for patients with FH,[116] especially for those with HoFH. This treatment can reduce LDL-C levels by 55%-70%. Long-term treatment can cause a reduction of skin xanthomas. The best treatment frequency is once each week. Currently, however, treatments are typically performed once

every two weeks. Lipoprotein-plasma exchange can be persistently performed during pregnancy. This treatment measure is expensive, time-consuming, and risks infection. Adverse reactions include hypotension, abdominal pain, nausea, hypocalcemia, iron-deficiency anemia, and allergic reaction. However, with the development of science, technology, and materials, the incidence of relevant adverse reactions has already decreased.

11.2 Liver transplantation and other surgical treatments

Liver transplantation can significantly improve LDL-C levels. Although simple liver transplantation or liver transplantation combined with heart transplantation is a successful treatment strategy, many problems exist including many post-transplantation complications, high mortality rates, a lack of donors, and the lifetime administration of immunosuppressive agents. Therefore, this treatment is rarely performed in clinical practice. Although partial ileal bypass surgery and portacaval shunt are not recommended, they should be considered when more effective treatment is lacking for patients with severe HoFH.[116]

12 Management of dyslipidemia in special populations

12.1 Diabetes

The major presentations of diabetes combined with dyslipidemia are increased TG, decreased HDL-C, and increased or normal LDL-C.[117] Lipid-lowering treatment can significantly reduce the risk of developing cardiovascular events in patients with diabetes.[61] The target level of LDL-C should be confirmed based on the severity of cardiovascular risks.[118] Patients with diabetes aged 40 years or older should control their serum LDL-C levels below 2.6 mmol/L (100 mg/dL) and maintain their target values of HDL-C above 1.0 mmol/L (40 mg/dL). The principle of dyslipidemia treatment in patients with diabetes follows the ASCVD risk assessment flow chart (Figure 3) for intervention management. According to the features of dyslipidemia, the preferred choice is statin therapy. If patients have combined high TG levels or do not have combined low HDL-C levels, a combination application of statins and fibrates can be used.

12.2 Hypertension

For patients with hypertension and dyslipidemia, lipidlowering treatments should be applied to determine lipidlowering target values according to different risk levels (Figure 3). Lipid-lowering treatments enable most patients with hypertension to obtain adequate benefits. The results are often more prominent with regard to the reduction of coronary heart disease events.[66] Therefore, the hypertension guidelines recommend that patients with hypertension and medium risk should initiate statin therapy. The newly released HOPE-3 study results suggest that statin therapy significantly reduces cardiovascular events for people at medium risk.[119,120] For the subgroup population with systolic pressure >143.5 mmHg, the combined application of statins and antihypertensive drugs reduces cardiovascular risks more significantly.

12.3 Metabolic syndrome

Metabolic syndrome is a group of clinical conditions that combine the development of obesity, high blood glucose (sugar regulation impairment or diabetes), hypertension, and dyslipidemia (hypertriglyceridemia, HDL-C hypolipidemia, or both). One feature is the combination of interrelated risk factors in the body metabolism of the same individual. These factors directly promote ASCVD development and increase the risk of developing type 2 diabetes. Some evidence indicates that patients with metabolic syndrome are most likely to develop cardiovascular disease. Compared with people without metabolic syndrome, their risks for developing cardiovascular disease and type 2 diabetes are significantly increased. [121]

The current cutoff points for determining the hyperglycemia, hypertension, and dyslipidemia aspects of metabolic syndrome were reached via a worldwide consensus. However, the core indicator of metabolic syndrome, obesity (especially central obesity), has different diagnostic criteria. The diagnostic criteria of metabolic syndrome formulated based on study evidence taken from the Chinese population should include three or more of the following items: (1) Central obesity/abdominal obesity: a waist circumference for men of ≥ 90 cm and that for women of ≥ 85 cm; (2) Hyperglycemia: fasting blood glucose ≥ 6.10 mmol/L (110 mg/dL) or 2-h blood glucose after glycemic load ≥ 7.80 mmol/L (140 mg/dL) or patients with confirmed diabetes who have received treatment; (3) Hypertension: blood pressure ≥ 130/85 mmHg or patients with hypertension who have received treatment; (4) Fasting TG ≥ 1.7 mmol/L (150 mg/dL); and (5) Fasting HDL-C < 1.0 mmol/L (40 mg/dL).

The major goal of metabolic syndrome management is toprevent ASCVD and type 2 diabetes. Patients who already have ASCVD should seek to prevent cardiovascular events. Active and sustained lifestyle interventions are important measures to achieve these treatment goals. In principle, lifestyle treatments should be initiated first. If these goals cannot be achieved, then corresponding drug treatments should be adopted to target each component. The treatment goals for dyslipidemia in metabolic syndrome are LDL-C < 2.6 mmol/L (100 mg/dL), TG < 1.7 mmol/L (150 mg/dL), and HDL-C ≥ 1.0 mmol/L (40 mg/dL).

12.4 CKD

CKD is usually accompanied by dyslipidemia and can promote the development of ASCVD. No clinical study has investigated the LDL-C treatment goal of patients with CKD. Under the premise of tolerance, patients with CKD are advised to receive statin therapy. The treatment goals for patients with mild-to-moderate CKD are LDL-C < 2.6 mmol/L and non-HDL-C < 3.4 mmol/L; those for patients with severe CKD and CKD combined with hypertension or patients with diabetes are LDL-C < 1.8 mmol/L and non-HDL-C < 2.6 mmol/L. Medium-intensity statin therapy is recommended. When necessary, cholesterol absorption inhibitors are combined. For patients with end-stage renal disease (ESRD) and those receiving hemodialysis, the risks and benefits of cholesterol-lowering treatments should be assessed carefully. Drug selection and the setting of the LDL-C goal should be personalized.

Patients with CKD represent a population at high risk for statin-induced myopathy, especially when renal function has shown a progressive decline or the glomerular filtration rate (GFR) is < 30 mL/min per 1.73 m^2. In addition, the risk of disease development is closely associated with the statin dosage; therefore, the administration of large doses should be avoided. When LDL-C cannot reach the target level after treatment with medium-intensity statins, combination therapy with ezetimibe is recommended.[81] Fibrate drugs can increase creatinine levels; when combined with statins among patients with moderate-to-severe CKD, the risk of myopathy might be increased.

12.5 FH

FH is an autosomal dominant hereditary cholesterol metabolism disorder. The pathogenic mechanism of FH is the functional genetic mutations on the LDL-C receptor, and a small number of cases are caused by functional mutations on Apo B or PCSK9. The newly discovered mutations on the LDL-C receptor modulator gene also explain the development of FH. The prominent clinical manifestations are the significant increase of serum LDL-C levels and early-onset coronary heart disease (myocardial infarction or angina pectoris). According to dominant genetic characteristics, the clinical phenotypes of FH are divided into the homozygous type (HoFH) and the heterozygous type (HeFH). Cholesterol level screening shows that the serum TC level of HeFH is usually > 8.5 mmol/L (328 mg/dl), and the serum TC level of HoFH is usually >13.5 mmol/L (521 mg/dl). Left untreated, HeFH patients usually develop cardiovascular disease after 40 years (men) or 50 years (women) of age. HoFH patients typically develop severe cardiovascular disease during childhood, and the mortality rate from cardiovascular diseases in early adulthood is 100 times higher than that among non-FH patients.

The ultimate goal of FH treatment is to reduce the risk of ASCVD and decrease the development of fatal and disabling cardiovascular diseases.[116] One focus of treatment is that all patients with FH (including HoFH and HeFH patients) should make enhanced therapeutic lifestyle changes to their diets (i.e., reduce lipid and cholesterol intake and consume a comprehensive balanced diet), exercise, and behavioral habits (i.e., quit smoking and reduce body weight). In addition, the management of other risk factors (e.g., hypertension and diabetes) should be emphasized. Next, patients with FH should adhere to long-term statin therapy beginning in adolescence to significantly reduce the risk of ASCVD. The target level of lipid-lowering treatment is the same as that for people at high cardiovascular risk. LDL-C is reduced by 25% in people with low LDL-C receptors after receiving statin therapy but only by 15% in people without LDL-C receptors. In fact, patients with FH usually require combined treatment with two or more types of lipid-lowering drugs. Patients at very high cardiovascular risk whose cholesterol levels still do not reach target levels after a combined lipid-lowering treatment, especially those with disease in progress, should consider receiving lipoprotein-plasma exchange as an adjuvant therapy.

12.6 Stroke

Whether other evidence of combined treatments with atherosclerosis exists, the use of long-term statin therapy for patients with non-cardiogenic ischemic stroke or TIA is recommended to reduce the risk of stroke and cardiovascular events (Class I recommendation, Level A

evidence).[63] If the baseline LDL-C level of patients is ≥ 2.6 mmol/L (100 mg/dL), then evidence of the treatment effect of statins is clear; if the baseline level of LDL-C is < 2.6 mmol/L (100 mg/dl), then clinical evidence is lacking. For patients with ischemic stroke resulting from intracranial large atherosclerotic stenosis (stenosis rate: 70%-99%) or patients with TIA, the recommended target value is LDL-C <1.8 mmol/L (70 mg/dL; Class I recommendation, Level B evidence). The long-term administration of statin therapy is safe in general. For patients with non-cardiogenic ischemic stroke and a history of cerebral hemorrhage or patients with TIA, statins can be reasonably used after weighing the risks and benefits.

12.7 Elderly people

Elderly people ≥ 80 years old usually have many types of chronic diseases and take various types of drugs. Attention should be paid to the interaction among drugs and their adverse reactions. Most elderly patients have different degrees of liver and kidney dysfunction; therefore, the selection of doses of lipid-lowering drugs should be individualized. The initial dose should not be too high, and the doses of lipid-lowering drugs should be adjusted based on treatment effects; in addition, liver and kidney function and creatine kinase should be closely monitored. Because no randomized controlled studies regarding the target goals of statin therapy have been conducted among elderly patients, there are no special recommendations concerning these patients. Current studies indicate that elderly patients with hypercholesterolemia combined with cardiovascular disease or diabetes benefit from lipid-lowering therapy.

References

1 National Health and Family Planning Commission of the People's Republic of China. Report on conditions of nutrition and chronic diseases of Chinese residents (2015). People's Health Publishing House: Beijing, China, 2015.

2 Moran A, Gu D, Zhao D, et al. Future cardiovascular disease in China: markov model and risk factor scenario projections from the coronary heart disease policy model-china. Circ Cardiovasc Qual Outcomes 2010; 3: 243–252.

3 Ding W, Dong H, Mi J. [Prevalence of dyslipidemia in Chinese children and adolescents: A meta-analysis]. Zhonghua Liu Xing Bing Xue Za Zhi 2015; 36: 71–77. [Article in Chinese].

4 Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet 2005; 366: 1267–1278.

5 Ren J, Grundy SM, Liu J, et al. Long-term coronary heart disease risk associated with very-low-density lipoprotein cholesterol in Chinese: the results of a 15-Year Chinese Multi-Provincial Cohort Study (CMCS). Atherosclerosis 2010; 211: 327–332.

6 Wang M, Zhao D, Wang W, et al. [Serum triglyceride is an independent risk factor for acute coronary heart disease events in 35- to 64-year-old Chinese: A Chinese multi-provincial Cohort Study]. Zhonghua Xin Xue Guan Bing Za Zhi 2008; 36: 940–943. [Article in Chinese].

7 Li Y, Chen Z, Zhou B, et al. [The predictive effects of lipids and lipoproteins on the incidence of ischemic cardiovascular disease in a middle-aged Chinese population]. Zhonghua Xin Xue Guan Bing Za Zhi 2004; 32: 643–646. [Article in Chinese].

8 Li J, Wang Li, Mi S, et al. [Awareness rate, treatment rate, and control rate of dyslipidemia in Chinese adults, 2010]. Zhonghua Yu Fang Yi Xue Za Zhi 2012; 46: 687–691. [Article in Chinese].

9 Joint committee for developing Chinese guidelines on prevention and treatment of dyslipidemia in adults. [Chinese guidelines on the prevention and treatment of dyslipidemia in adults]. Zhonghua Xin Xue Guan Bing Za Zhi 2007; 35: 390-419. [Article in Chinese].

10 Wang Y, Liu J, Wang W, et al. Lifetime risk for cardiovascular disease in a Chinese population: the Chinese Multi-Provincial Cohort Study. Eur J Prev Cardiol 2015; 22: 380–388.

11 Jiang Z, Zhan S, Jia X, et al. Basic methods and procedures for development/amendment of clinical diagnosis and treatment guidelines. Chinese Med J 2016; 96: 250–253.

12 Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63: 2889–2934.

13 Reiner Z, Catapano AL, De Backer G, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the Management of Dyslipedemias of the Europe Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011; 32: 1769–1818.

14 Zhao SP. Articles on lipid research. Central South University Press: Changsha, China; 2014: 2–107.

15 Ballantyne CM. Clinical lipidology: a companion to Braunwald's heart disease, 2nd Edition. Philadelplia: Saunders: Philadelphia, USA, 2014.

16 Jacobson TA, Ito MK, Maki KC, et al. National lipid association recommendations for patient-centered management of dyslipidemia: part 1—full report. J Clin Lipidol 2015; 9: 129–169.

17 Yan S. The association between blood lipid tests and clinical results should be further strengthened. Chin J Clin Lab Sci 2008; 26: 243–245.

18 Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation 2011; 123: 2292–2333.

19 Gotto AM, Brinton EA. Assessing low levels of high-density lipoprotein cholesterol as a risk factor in coronary heart disease: a working group report and update. J Am Coll Cardiol 2004; 43: 717–724.

20 Luc G, Bard JM, Arveiler D, et al. Lipoprotein(a) as a predictor of coronary heart disease: The PRIME study. Athrosclerosis 2002; 163: 377–384.

21 Son JI, Chin SO, Woo JT. Treatment guidelines for dyslipidemia: summary of the expanded second version. J Lipid Atheroscler 2012; 1: 45–59.

22 Teramoto T, Sasaki J, Ishibashi S, et al. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. J Atheroscler Thromb 2013; 20: 517–523.

23 Zhao S. [Clinical manifestation and classification of hyperlipidemia]. Zhonghua Lin Chuang Yi Si Za Zhi 2003; 31: 23–24. [Article in Chinese].

24 Grundy SM. An international atherosclerosis society position paper: global recommendations for the management of dyslipidemia. J Clin Lipidol 2013; 7: 561–565.

25 Najam O, Ray KK. Familial hypercholesterolemia: a review of the natural history, diagnosis, and management. Cardiol Ther 2015; 4: 25–38.

26 Hegele RA, Ginsberg HN, Chapman MJ, et al. The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management. Lancet Diabetes Endocrinol 2014; 2: 655–666.

27 Wu Y, Zhao D, Zhou B, et al. [The cutoffs and risk stratification of dyslipidemia in Chinese adults]. Zhonghua Xin Xue Guan Bing Za Zhi 2007; 35: 428–433. [Article in Chinese].

28 Zhao D, Liu J, Xie W, et al. Cardiovascular risk assessment: a global perspective. Nat Rev Cardiol 2015; 12: 301–311.

29 Wang W, Zhao D, Liu J, et al. [Serum total cholesterol and 10-year cardiovascular risk in a Chinese cohort aged 35–64 years]. Zhonghua Xin Xue Guan Bing Za Zhi 2006; 34: 169–173. [Article in Chinese].

30 Lui J, Zhao D, Qin L, et al. [The association of low-density lipoprotein cholesterol with cardiovascular disease in a prospective study]. Zhonghua Xin Xue Guan Bing Za Zhi 2001; 29: 561–565. [Article in Chinese].

31 Pencina MJ, D'Agostino RB, Larson MG, et al. Predicting the 30-year risk of cardiovascular disease: the Framingham heart study. Circulation 2009; 119: 3078–3084.

32 Grundy SM, Arai H, Barter P, et al. An international atherosclerosis society position paper: global recommendations for the management of dyslipidemia—full report. J Clin Lipidol 2014; 8: 29–60.

33 Jellinger PS, Smith DA, Mehta AE, et al. American association of clinical endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. Endocr Pract 2012; 18(Suppl 1): S1–S78.

34 Anderson TJ, Gregoire J, Hegele RA, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol 2013; 29: 151–167.

35 Rabar S, Harker M, O' Flynn N, et al. Lipid modification and cardiovascular risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. BMJ 2014; 349: g4356.

36 Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation 2006; 113: 791–798.

37 Lloyd-Jones DM, Wilson PW, Larson MG, et al. Framingham risk score and prediction of lifetime risk for coronary heart disease. Am J Cardiol 2004; 94: 20–24.

38 Hu D. [It is difficult to lower low-density lipoprotein cholesterol]. Zhonghua Xin Xue Guan Bing Za Zhi 2015; 43: 3–4, 39. [Article in Chinese].

39 Zhao S, Huang S, Hu D. [A comparison between the ACC/AHA and ESC/EAS blood-lipid guidelines]. Zhonghua Xin Xue Guan Bing Za Zhi 2014; 42: 898–899. [Article in Chinese].

40 Sun Y, Hu D. [How to understand the evidence and benefits of enhanced doses of statin?] Zhonghua Xin Xue Guan Bing Za Zhi 2014; 42: 899–901. [Article in Chinese].

41 Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015; 372: 2387–2397.

42 Dai W, Huang XS, Zhao SP. No evidence to support highintensity statin in Chinese patients with coronary heart disease. Int J Cardiol 2016; 204: 57–58.

43 HPS2-THRIVE Collaborative Group. HPS2-THRIVE randomized placebo-controlled trial in 25673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. Eur Heart J 2013; 34: 1279–1291.

44 Zhao SP, Wang Y, Mu Y, et al. Prevalence of dyslipidaemia in patients treated with lipid-lowering agents in China: results of the DYSlipidemia International Study (DYSIS). Atherosclerosis 2014; 235: 463–469.

45 Zhao SP, Peng DQ, Yu BL, et al. The effect of moderatedose versus double-dose statins on patients with acute coronary syndrome in China: Results of the CHILLAS trial. Atherosclerosis 2014; 233: 707–712.

46 Chinese Society of Cardiology. [Correct understanding the rational use of lipid lowering drugs]. Zhonghua Xin Xue Guan Bing Za Zhi 2001; 29: 705–706. [Article in Chinese].

47 Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4,444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383–1389.

48 Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. N Engl J Med 1996; 335: 1001–1009.

49 Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339: 1349–1357.

50 Serruys PW, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following successful first percutaneous coronary intervention—A randomized controlled trial. JAMA 2002; 287: 3215–3222.

51 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7–22.

52 Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350: 1495–1504.

53 de Lemos JA, Blazing MA, Wiviott SD, et al. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004; 292: 1307–1316.

54 LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352: 1425–1435.

55 Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. JAMA 2001; 285: 1711–1718.

56 Pedersen TR, Faergeman O, Kastelein JJ, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005; 294: 2437–2445.

57 Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010; 376: 1670-1681.

58 Nissen SE, Nicholls SJ, Sipahi I, et al. Effect of very highintensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006; 295: 1556–1565.

59 Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995; 333: 1301–1307.

60 Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. JAMA 1998; 279: 1615–1622.

61 Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo controlled trial. Lancet 2004; 364: 685–696.

62 Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008; 359: 2195–2207.

63 Amarenco P, Bogousslavsky J, Callaham A, et al. High-dose atorvastatin after stroke ortransient ischemic attack. N Engl J Med 2006; 355: 549–559.

64 Shepherd J, Blauw GJ, Murphy MB, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002; 360: 1623–1630.

65 The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipd-lowering treatment to prevent heart attack trial (ALLHAT-LLT). JAMA 2002; 288: 2998–3007.

66 Sever PS, Dahlof B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicenter randomised controlled trial. Lancet 2003; 361: 1149–1158.

67 Chen H, Ren, We B, et al. [The effects after withdrawal of simvastatin on brachial artery endothelial function in patient with coronary heart disease or risk factors]. Zhonghua XinXue Guan Bing Za Zhi 2007; 35: 531–535. [Article in Chinese].

68 Li JJ, Yang P, Liu J, et al. The effect of 10 mg rosuvastatin daily or alternate-day on lipid profile and inflammatory markers. Clin Chim Acta 2012; 413: 139–142.

69 Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomized trials. Lancet 2012; 380: 581–590.

70 [Collaborative Group on the adjustment of blood lipids by Xuezhikang on the secondary prevention of coronary heart disease]. Zhonghua Xin Xue Guan Bing Za Zhi 2005; 33: 109–115. [Article in Chinese].

71 Lu Z, Kou W, Du B, et al. The effect of Xuezhikang, an extract from red yeast Chinese rice, on the coronary events in a Chinese population with previous myocardial infarction.Am J Cardiol 2008; 101: 1689–1693.

72 Li JJ, Lu ZL, Kou WR, et al. Impact of Xuezhikang on coronary events in hypertensive patients with previous myocardial infarction from the China Coronary Secondary Prevention Study (CCSPS). Ann Med 2010; 42: 231–240.

73 Zhao SP, Liu L, Cheng YC, et al. Xuezhikang, an extract of cholestin, protects endothelial function through anti-inflammatory and lipid-lowering mechanisms in patients with coronary heart disease. Circulation 2004; 110: 915–920.

74 McKenney JM, Davidson MH, Jacobson TA, et al. Final conclusions and recommendations of the national lipid association statin safety assessment task force. Am J Cardiol 2006; 97: 89C–94C.

75 Bays H, Cohen DE, Chalasani N, et al. An assessment by the statin liver safety task force: 2014 update. J Clin Lipidol 2014; 8: S47–S57.

76 Rosenson RS, Baker SK, Jacobson TA, et al. An assessment by the statin muscle safety task force: 2014 update. J Clin Lipidol 2014; 8(3 Suppl): S58–S71.

77 Stroes ES, Thompson PD, Corsini A, et al. Statin-associated muscle symptoms: impact on statin therapy—European Atherosclerosis Society consensus panel statement on assessment, aetiology and management. Eur Heart J 2015; 36: 1012–1022.

78 Maki KC, Ridker PM, Brown WV, et al. An assessment by the statin diabetes safety task force: 2014 update. J Clin Lipidol 2014; 8(3 Suppl): S17–S29.

79 Rojas-Fernandez CH, Goldstein LB, Levey AI, et al. An assessment by the statin cognitive safety task force: 2014 update. J Clin Lipidol 2014; 8(3 Suppl): S5–S16.

80 Geng Q, Ren JY, Song JX, et al. Meta-analysis of the effect of statins on renal function. Am J Cardiol 2014; 114: 562–570.

81 Sharp Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J 2010; 160: 785–794.

82 Yamashita S, Hbujo H, Arai H, et al. Long-term probucol treatment prevents secondary cardiovascular events: a cohort study of patients with heterozygous familial hypercholesterolemia in Japan. J Atheroscler Thromb 2008; 15: 292–303.

83 Yamashitaa S, Matsuzawab Y. Where are we with probucol: A new life for an old drug? Atherosclerosis 2009; 207: 16–23.

84 Knapp HH, Schrott H, Ma P, et al. Efficacy and safety of combination simvastatin and colesevelam in patients with primary hypercholesterolemia. Am J Med 2001; 110: 352–360.

85 Xu DY, Shu J, Huang QY, et al. Evaluation of the lipid lowering ability, anti-inflammatory effects and clinical safety of intensive therapy with Zhibitai, a Chinese traditional medicine. Atherosclerosis 2010; 211: 237–241.

86 Xu D, Shu J, Huang Q, et al. [A comparative study of the efficacy and safety Zhibitai and atorvastatin]. Zhonghua Nei Ke Za Zhi 2010; 49: 392–395. [Article in Chinese].

87 Liu S, Tan M, Zhao S, et al. [The effects of policosanol on serum lipids and heme oxygenase-1 in patients with hyperlipidemia]. Zhonghua Xin Xue Guan Bing Za Zhi 2012; 40: 840–843. [Article in Chinese].

88 Expert consensus group on the clinical application of policosanol. [Expert consensus on the clinical application of a new type of plant lipid-lowering drug (policosanol)]. Zhonghua Nei Ke Za Zhi 2008; 47: 961–963. [Article in Chinese].

89 Rubins HB, Robins SJ, Collins D, et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. N Engl J Med 1999; 341: 410–418.

90 Keech A, Simes RJ, Barter P, et al. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomized controlled trial. Lancet 2005; 366: 1849–1861.

91 Ginsberg HN, Elam MB, Lovato LC, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 2010; 362: 1563–1574.

92 Jun M, Foote C, Lv J, et al. Effects of fibrates on cardiovascular outcomes: a systematic review and meta-analysis. Lancet 2010; 375: 1875–1884.

93 Zhu C, Ye P, Kou W, et al. [A survey on the efficacy and tolerability of micronized fenofibrate in patients with dyslipidemia]. Zhonghua Xin Xue Guan Bing Za Zhi 2002; 30: 152–155. [Article in Chinese].

94 Lavigne PM, Karas RH. The current state of niacin in cardiovascular disease prevention: A systematic review and metaanalysis. J Am Coll Cardiol 2013; 61: 440–446.

95 Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011; 365: 2255–2267.

96 Landray MJ, Haynes R, Hopewell JC, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014; 371: 203–212.

97 Leaf A, Weber PC. Cardiovascular effects of n-3 fatty acids. N Engl J Med 1988; 318: 549–557.

98 Harris WS. n-3 fatty acids and serum lipoproteins: human studies. Am J Clin Nurr 1997; 65(5 Suppl): 1645S–1654S.

99 Harris WS. n-3 fatty acids and lipoproteins: comparison of results from human and animal studies. Lipids 1996; 31: 243–252.

100 GISSI-Preventione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevention trial, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet 1999; 354: 447–455.

101 Kromhout D, Giltay EJ, Geleijnse JM, et al. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 2010; 363: 2015–2026.

102 Risk and Prevention Study Collaborative Group. n-3 fatty acids in patients with multiple cardiovascular risk factors. N Engl J Med 2013; 368: 1800–1808.

103 Cuchel M, Meagher EA, du TTH, et al. Efficacy and safety of a microsomal triglyceride transfer protein inhibitor in patients with homozygous familial hypercholesterolaemia: a single-arm, open-label, phase 3 study. Lancet 2013; 381: 40–46.

104 Rader DJ, Kastelein JJ. Lomitapide and mipomersen: two first-in-class drugs for reducing low-density lipoprotein cholesterol in patients with homozygous familial hypercholesterolemia. Circulation 2014; 129: 1022–1032.

105 Raal FJ, Santos RD, Blom DJ, et al. Mipomersen, an apolipoprotein B synthesis inhibitor, for lowering of LDL cholesterol concentrations in patients with homozygous familial hypercholesterolaemia: a randomised, double-blind, placebo-controlled trial. Lancet 2010; 375: 998–1006.

106 Stein EA, Mellis S, Yancopoulos GD, et al. Effect of a monoclonal antibody to PCSK9 on LDL cholesterol. N Engl J Med 2012; 366: 1108–1118.

107 Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 2015; 372: 1500-1509.

108 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: 1489–1499.

109 Ballantyne CM, Weiss R, Moccetti T, et al. Efficacy and safety of rosuvastatin 40 mg alone or in combination with ezetimibe in patients at high risk of cardiovascular disease (results from the EXPLORER study). Am J Cardiol 2007; 99: 673–680.

110 Mikhailidis DP, Sibbring GC, Ballantyne CM, et al. Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy. Curr Med Res Opin 2007; 23: 2009–2026.

111 Ballantyne CM, Houri J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003; 107: 2409–2415.

112 Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 2002; 40: 2125–2134.

113 Melani L, Mills R, Hassman D, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J 2003; 24: 717–728.

114 Jones PH, Davidson MH, Goldberg AC, et al. Efficacy and safety of fenofibric acid in combination with a statin in patients with mixed dyslipidemia: Pooled analysis of three phase 3, 12-week randomized, controlled studies. J Clin Lipidol 2009; 3: 125–137.

115 Ren J, Chen H, Luo Y. [Efficacy and safety of combination therapy with simvastatin and fenofibrate for combined hyperlipidemia]. Zhonghua Xin Xue Guan Bing Za Zhi 2005; 33: 122–126. [Article in Chinese].

116 Cuchel M, Bruckert E, Ginsberg HN, et al. Homozygous familial hypercholesterolaemia: New insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society. Eur Heart J 2014; 35: 2146–2157.

117 American Diabetes Association. Dyslipidemia management in adults with diabetes. Position statement & ADA statement. Diabetes Care 2004; 27(Suppl): S68–S71.

118 Chinese Diabetes Society. Guidelines for the prevention and treatment of type 2 diabetes in China (2013 edition). Zhonghua Tang Niao Bing Za Zhi 2014; 6: 447–498.

119 Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in people at intermediate risk but without cardiovascular disease. New Engl J Med 2016; 374: 2021–2031

120 Yusuf S, Lonn E, Pais P, et al. Blood-pressure and cholesterol lowering in persons without cardiovascular disease. New Engl J Med 2016; 374: 2032–2043.

121 Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome. An AHA/NHLBI scientific statement. Circulation 2005; 112: 2735–2752.

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10.8 Appendix 8: Abbreviations

Abbreviation	Expanded Term
AE	adverse event
ALT	alanine transaminase
APaT	All Participants as Treated
ASCVD	atherosclerotic cardiovascular disease
AST	aspartate transaminase
β-hCG	β-human chorionic gonadotropin
BMI	body mass index
CABG	coronary artery bypass graft
CAC	Clinical Adjudication Committee
CHD	coronary heart disease
CK	creatine kinase
CKD	chronic kidney disease
CRF	Case Report Form
CSR	Clinical Study Report
CTFG	Clinical Trial Facilitation Group
CYP3A4	cytochrome P-450 3A4
DILI	drug-induced liver injury
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECI	event of clinical interest
eCRF	electronic Case Report Form
EDC	electronic data collection
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOC	Executive Oversight Committee
FAS	Full Analysis Set
FDAAA	Food and Drug Administration Amendments Act
FDC	Fixed Dose Combination
FSH	Follicle stimulating hormone
fT4	Free thyroxin
GCP	Good Clinical Practice
HDL-C	high-density lipoprotein cholesterol
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
INR	International Normalized Ratio

Abbreviation	Expanded Term
IRB	Institutional Review Board
IRT	interactive response technology
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IVRS	interactive voice response system
IWRS	integrated web response system
LDL-C	low-density lipoprotein cholesterol
MI	myocardial infarction
NYHA	New York Heart Association
NIMP	Non-Investigational Medicinal Product
NPC1L1	Niemann-Pick Cl Like 1
OTC	over the counter
PCI	percutaneous coronary intervention
PIN	participant identification number
PK	pharmacokinetic
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
SoA	schedule of activities
sSAP	supplemental SAP
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TC	total cholesterol
TG	triglyceride
TSH	thyroid stimulating hormone
ULN	Upper Limit Of Normal
WOCBP	woman/women of childbearing potential

11 REFERENCES

[Ballantyne, C. M., et al 2003]	Ballantyne CM, Houri J, Notarbartolo A, Melani L, Lipka LJ, Suresh R, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003;107:2409-15.	03PHZ3
[Ballantyne, C. M., et al 2005]	Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: The Vytorin Versus Atorvastatin (VYVA) Study. Am Heart J 2005;149(3):464-73.	02TNST
[Barquera, S., et al 2015]	Barquera S, Pedroza-Tobias A, Medina C, Hernandez-Barrera L, Bibbins-Domingo K, Lozano R, et al. Global overview of the epidemiology of atherosclerotic cardiovascular disease. Arch Med Res. 2015;46:328-38.	04ZVDQ
[Benjamini, Y. and Hochberg, Y. 1995]	Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J R Stat Soc Series B Stat Methodol 1995;57(1):289-300.	03Q07Y
[Cannon, C. P., et al 2015]	Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015 Jun 18;372(25):2387-97.	048T6N
[Castelli, W. P., et al 1983]	Castelli WP, Abbott RD, McNamara PM. Summary estimates of cholesterol used to predict coronary heart disease. Circulation 1983;67(4):730-4.	03PWCM
[Catapano, A., et al 2005]	Catapano A, Brady WE, King TR, Palmisano J. Lipid altering-efficacy of ezetimibe co-administered with simvastatin compared with rosuvastatin: a meta-analysis of pooled data from 14 clinical trials. Current Medical Research and Opinion 2005;21(07):1123-30.	02SQT7

[Chen, Z., et al 1991]	Chen Z, Peto R, Collins R, MacMahon S, Lu J, Li W. Serum cholesterol concentration and coronary heart disease in population with low cholesterol concentrations. BMJ 1991;303:276-82.	03PFQ4
[Cheong, C., et al 2008]	Cheong C, Barner JC, Lawson KA, Johnsrud MT. Patient adherence and reimbursement amount for antidiabetic fixed-dose combination products compared wtih dual therapy among Texas Medicaid recipients. Clin Ther 2008;30(10):1893-907.	03R6FJ
[Conard, Scott E., et al 2008]	Conard SE, Bays HE, Leiter LA, Bird SR, Rubino J, Lowe RS, et al. Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) versus uptitration of atorvastatin (to 40 mg) in hypercholesterolemic patients at moderately high risk for coronary heart disease. Am J Cardiol 2008;102(11):1489-94.	03QR00
[Davidson, M. H., et al 2002]	Davidson MH, McGarry T, Bettis R, Melani L, Lipka LJ, LeBeaut AP. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 2002;40(12):2125-2134i.	03PGGL
[Goldberg, A. C., et al 2004]	Goldberg AC, Sapre A, Liu J, Capece R, Mitchel YB. Efficacy and safety of ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia: a randomized double-blind, placebo-controlled trial. Mayo Clin Proc 2004;79:620-9.	02S5HD
[Gould, A. L., et al 1998]	Gould AL, Rossouw JE, Santanello NC, Heyse JF, Furberg CD. Cholesterol reduction yields clinical benefit: impact of statin trials. Circulation 1998;97:946-52.	03NZ6V
[Grigore, L., et al 2008]	Grigore L, Norata GD, Catapano AL. Combination therapy in cholesterol reduction: focus on ezetimibe and statins. Vasc Health Risk Manag. 2008;4(2):267-78.	04ZW85

[Grundy, S. M., et al 2004]	Grundy SM, Cleeman JI, Merz CNB, Brewer HB, Clark LT, Hunninghake DB, et al. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. Circ J 2004;110:227-39.	03MZ6L
[Haque, T. 2010]	Haque T, Khan BV. Atorvastatin: a review of its pharmacological properties and use in familial hypercholesterolemia. Clin. Lipidol. 2010;5(5):615:25.	04ZW7D
[IMS Health 2006]	IMS Health. Commonly requested therapeutic class and product information (updated February 2006). 2006	03QVHG
[Ingersoll, K. S. and Cohen, J. 2008]	Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med 2008;31:213-24.	03QPC8
[Kannel, W. B., et al 1979]	Kannel WB, Castelli WP, Gordon T. Cholesterol in the prediction of atherosclerotic disease. New perspectives based on the Framingham study. Ann Intern Med. 1979 Jan;90(1):85-91.	04FVTG
[Leiter, Lawrence A., et al 2008]	Leiter LA, Bays H, Conard S, Bird S, Rubino J, Hanson ME, et al. Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with uptitration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease. Am J Cardiol 2008;102(11):1495-501.	03QR02
[Li, Q., et al 2017]	Li Q, Wu H, Yue W, Dai Q, Liang H, Bian H, et al. Prevalence of stroke and vascular risk factors in China: a nationwide community-based study. Sci Rep. 2017 Jul 25;7:6402.	04ZVDX
[Liang, Kung-Yee and Zeger, Scott L. 2000]	Liang K-Y, Zeger SL. Longitudinal data analysis of continuous and discrete responses for pre-post designs. Sankhya: The Indian Journal of Statistics 2000;62(Series B, Pt. 1):134-48.	00QJ0M

[Miettinen, Olli and Nurminen, Markku 1985]	Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.	00QHZT
[Mikhailidis, D. P., et al 2009]	Mikhailidis DP, Sibbring GC, Ballantyne CM, Davies GM, Catapano AL. Meta-analysis of the cholesterol-lowering effect of ezetimibe added to ongoing statin therapy. Curr Med Res Opin. 2007;23(8):2009-26.	04ZW82
[Moran, A., et al 2010]	Moran A, Gu D, Zhao D, Coxson P, Wang YC, Chen CS, et al. Future cardiovascular disease in China: Markov model and risk factor scenario projections from the coronary heart disease policy model-China. Circ Cardiovasc Qual Outcomes. 2010 May;3:243-52.	050J0H
[Okamura, T., et al 2007]	Okamura T, Tanaka H, Miyamatsu N, Hayakawa T, Kadowaki T, Kita Y, et al. The relationship between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. Atherosclerosis. 2007;190:216-23.	04ZSW9
[Pearson, T. A., et al 2005]	Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clin Proc 2005;80(5):587-95.	03QXNT
[Ren, J., et al 2010]	Ren J, Grundy SM, Liu J, Wang W, Wang M, Sun J, et al. Long-term coronary heart disease risk associated with very-low-density lipoprotein cholesterol in Chinese: the results of a 15-Year Chinese Multi-Provincial Cohort Study (CMCS). Atherosclerosis. 2010;211:327-32.	04ZVXR
[Shroufi, A. 2010]	Shroufi A, Powles JW. Adherence and chemoprevention in major cardiovascular disease: a simulation study of the benefits of additional use of statins. J Epidemiol Community Health. 2010;64:109-13.	04ZSZL

[Stamler, J., et al 1986]	Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded?: findings in 356 222 primary screenees of the multiple risk factor intervention trial (MRFIT). JAMA 1986;256(20):2823-8.	03P6FS
[Stamler, J., et al 1986]	Stamler J, Wentworth D, Neaton JD. Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? JAMA 1986;256(20):2823-8.	03NSRK
[Stein, E., et al 2004]	Stein E, Stender S, Mata P, Sager P, Ponsonner D, Melani L, et al. Achieving lipoprotein goals in patients at high risk with severe hypercholesterolemia: Efficacy and safety of ezetimibe co-administered with atorvastatin. Am Heart J 2004;148(3):447-55.	03PV36
[Szatrowski, T. P., et al 1984]	Szatrowski TP, Peterson AV, Jr., Shimizu Y, Prentice RL, Mason MW, Fukunaga Y, et al. Serum cholesterol, other risk factors, and cardiovascular disease in a Japanese cohort. J Chronic Dis 1984;37(7):569-84.	03QBGC
[Teramoto, T., et al 2012]	Teramoto T, Sawada T, Iwamoto K, Daida H. Clinical efficacy and tolerability of ezetimibe in combination with atorvastatin in Japanese patients with hypercholesterolemia-ezetimibe phase IV randomized controlled trial in patients with hypercholesterolemia. Curr Ther Res Clin Exp. 2012 Feb;73(1-2):16-40.	04923J
[Toth, P. P., et al 2010]	Toth PP, Catapano A, Tomassini JE, Tershakovec AM. Update on the efficacy and safety of combination ezetimibe plus statin therapy. J Clin Lipidol 2010;5(5):655-84.	03RM7P
[UK Summary of Product Characteristics 2013]	UK Summary of Product Characteristics: Ezetrol 10mg Tablets: 2013.	03RSCG
[US Prescribing Information 2013]	US Prescribing Information: Zetia (ezetimibe) tablets: February 2013.	03RRY7

[Van Heek, M. and Davis, H. 2002]	Van Heek M, Davis H. Pharmacology of ezetimibe. Eur Heart J Suppl 2002;4:J5-J8.	03PFQQ
[Wong, P., et al 1999]	Wong P, Mukhopadhyay S, Quan H, Larson P. Confidence intervals for between-treatment mean difference when analysis is on the log percent scale. American Statistical Association, 1999 Proceedings of the Biopharmaceutical Section, 1999:111-6.	03NZLF
[Yang, G., et al 2013]	Yang G, Wang Y, Zeng Y, Gao GF, Liang X, Zhou M, et al. Rapid health transition in China, 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2013 Jun 8;381:1987-2015.	04ZV5T
[Zhou, M., et al 2016]	Zhou M, Wang H, Zhu J, Chen W, Wang L, Liu S, et al. Cause-specific mortality for 240 causes in China during 1990-2013: a systematic subnational analysis for the Global Burden of Disease Study 2013. Lancet. 2016 Jan 16;387:251-72.	04ZV6M