Protocol

LODESTAR Protocol and Statistical analysis plan

1. First version (31 August 2015) of the LODESTAR protocol

Comparing the Intensity-based statin therapy with attained low-density lipoprotein cholesterol based statin therapy in patients with coronary artery disease: Statin Strategy Proposal

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Initial version (August 31, 2015)

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Protocol

1. Protocol Summary

Title of Study	Comparing the Intensity-based statin therapy with attained low-density lipoprotein cholesterol based statin therapy in patients with coronary artery disease: Statin Strategy Proposal
Study Centers	Division of Cardiology, Yonsei Cardiovascular Hospital, Yonsei University College of Medicine
Phase of Development	Phase IV
Objective	To compare clinical safety & efficacy of targeting LDL-C level <70 mg/dL statin therapy (statin therapy with target group; according to 2013 ACC/AHA guideline) versus non-targeting LDL-C level high-intensity statin therapy (high-intensity statin therapy without target group) in patients with coronary artery disease for secondary prevention.
Methodology	Prospective, open label, randomized study
Number of Subjects	Total 4400 patients with coronary artery disease patients requiring statin treatment
Study Design	• Prospective, open label, randomized, multicenter study • Randomization with a 1:1 to either of statin therapy with target group or high-intensity statin therapy without target group • Randomized stratification according to baseline LDL-C, presence of diabetes mellitus, and acute coronary syndrome • Additional allocation to rosuvastatin or atorvastatin within each group • Clinical follow-up for 36 months
Diagnosis and Main Criteria for Inclusion	• Patients ≥ 19 years old • Patients clinically diagnosed with coronary artery disease including stable angina, unstable angina, acute non-ST elevation myocardial infarction and acute ST elevation myocardial infarction • Patients with signed informed consent
Primary and Major Secondary Endpoints	• **Primary endpoint:** Major Adverse Cardiac and Cerebrovascular Event (MACCE); Clinical outcomes composed of death from any cause, myocardial infarction, stroke, and revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting • **Secondary endpoint:**

	1. New onset diabetes mellitus after randomization 2. Hospitalization due to heart failure 3. Deep vein thrombosis or pulmonary thromboembolism 4. Percutaneous trans-luminal angioplasty on peripheral artery obstructive disease 5. Aortic intervention or operation 6. End-stage renal disease 7. The rate of statin treatment discontinuation 8. Composite of laboratory abnormality: - Aminotransferase elevation: (ALT > 3 x ULN) - Creatine kinase elevation: (CK>5 x ULN) - Increase of creatinine
Statistical Methods	Clinical outcome (MACCE) and adverse events - Cumulative incidence using Kaplan-Meier method - Log-rank test - Cox proportional hazard regression model
Study Duration	Overall study will require 60 months to complete, including 24 months of recruitment and 36 months of follow-up followed by close out and reporting of final results.
Participating Sites	1. Yonsei University Severance Hospital 2. Gangnam Severance Hospital 3. Inje University Sanggye Paik Hospital 4. Inje University Ilsan Paik Hospital 5. Myong Ji Hospital 6. Sejong General Hospital 7. Gachon University Gil medical Center 8. Seoul Eulji Hospital 9. Intl. St. Mary`s Hospital 10. Jeju national University Hospital

2. BACKGROUND

Almost one-third of the population will die as a result of heart attack or stroke associated with atherosclerotic cardiovascular disease (ASCVD), the leading cause of death and disability today (1). The major treatable causes of ASCVD include hypercholesterolemia, hypertension, diabetes, and an unhealthy lifestyle. Over the past 3 decades, on the basis of observational studies and some randomized controlled trials (RCTs), guideline recommendations have been developed focusing on treatment strategies to reduce these risk factors. Because low-density lipoprotein (LDL) plays a significant role in the promotion, development, and progression of vascular atherosclerosis, a primary strategy in these efforts has been lowering of LDL cholesterol in at-risk populations (2). Hydroxymethylglutaryl-CoA reductase inhibitor, statin, has beneficial properties include atherosclerotic plaque stabilization, oxidative stress reduction, enhancement of endothelial function and a decrease in vascular inflammation beyond their lipid-lowering effect (3). In various clinical trials, statins have shown clinical benefits in primary and secondary prevention (4-6). Epidemiological studies demonstrate a continuous relationship between cholesterol levels and ASCVD risk, from low to high (7). RCTs show the reverse: the more LDL-C is lowered, the greater the risk reduction (8, 9). Furthermore, there appears to be no limit beneath which a lower LDL-C fails to reduce risk. Meta-analysis of statin trials show that risk reduction extends into the very low range for LDL-C (10). Thus, it can be said that “the lower, the better” is true for cholesterol reduction.

The NCEP ATP III guideline and 2004 update have served as the standard of care for at-risk patients with hyperlipidemia for nearly a decade (11). Guideline focused on the fasting lipid panel as the initial evaluation of lipid-related CVD risk. Within each category of ASCVD risk, targets of treatment are then specified in these recommendations. In the ATP III guidelines, cardiovascular disease (CVD) and diabetes mellitus (DM) as a coronary heart disease (CHD) risk equivalent were considered as high-risk category. LDL-C was considered the primary target of therapy and an optional goal of LDL-C < 70mg/dl in these high–risk patients. The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias define documented cardiovascular disease, previous myocardial infarction, coronary revascularization, ischemic stroke, DM with target organ damage, or moderate to severe CKD as very high-risk group and recommended target LDL -C level of <70mg/dL and/or ≥50% LDL-C reduction when target level cannot reach (12).

To update previous guideline recommendations, the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adult was recently issued (13). For processing this new guideline, it was unable to find RCT evidence to support continued use of specific LDL-C and/or non-HDL-C targets. In other words, use of LDL-C targets may result in under-treatment with evidence-based statin therapy or overtreatment with non-statin drugs that have not been shown to reduce ASCVD events in RCT. On the basis of evidence, 4 major statin benefit groups were identified: 1) with clinical ASCVD, 2) primary elevations of LDL-C≥190mg/dL, 3) diabetes age 40-75 years with LDL-C 70-189 and without clinical ASCVD, or 4) estimated 10-year ASCVD risk ≥7.5% by new Pooled Cohort Equations. For these groups, the new guideline proposes that implementation of cholesterol-lowering treatment using evidenced-based intensity of statin therapy should be treated in patients without such targets.

There are several concerns about using fixed-high potent statin following new guideline, especially for Asian population. First, statin potency from recent issued guideline was set from the studies composed of mainly Caucasian population (14). In addition, there was an inconsistency of efficacy of statin according to ethnic population. Asian population showed more profound LDL reduction not only from high potent statin but from moderate to low potent statin (15). Second, there is increased risk of adverse effects on high intensity statin therapy. For example, statin therapy modestly increases the risk for developing type 2 diabetes. The risk is lower for moderate-intensity statins (approximately 0.1 excess case of diabetes per 100 statin-treated patients/year) than for high-intensity statins (approximately 0.3 excess case of diabetes per 100 statin-treated patients/year) (16, 17).

It is no surprise that a revolutionary change from decades of emphasis on LDL-C goals of therapy in dyslipidemia would generate considerable controversy and confusion. These were due to substantive differences in both the process of guideline development and the content of the new ACC/AHA clinical practice recommendations. The 2013 ACC/AHA Guidelines are narrower in scope and consider 3 critical questions in lipid management for ASCVD prevention. They provide discussion of evidence but limited recommendations for the treatment of special populations (e.g., age <40 to >75 years; Asian ethnic populations) and management of patients with complex dyslipidemias, suboptimal response to therapy, adverse effects on statin therapy, or complete statin intolerance.

There are these limitations according to the guidelines and there is no direct data from RCTs that compare the efficacy of the targeted LDL-C statin therapy and the non-targeted high-intensity statin therapy until now. Therefore, we will evaluate the clinical validity of the targeted LDL-C level (< 70 mg/dl) statin therapy for secondary prevention of ASCVD compared with the non-targeted LDL-C level high-intensity statin therapy in this study.

3. STUDY OBJECTIVES

The purpose of this study is to compare clinical efficacy and safety of targeting LDL-C level <70 mg/dL statin therapy (targeted statin group) *versus* non-targeting LDL-C level high-intensity statin therapy (non-targeted high-intensity statin group) in patients with coronary artery disease as a high ASCVD risk group.

3.1. Primary endpoint

Primary endpoint	Primary endpoint variable
Major Adverse Cardiac and Cerebrovascular Event (MACCE)	Clinical outcomes composed of death from any cause, myocardial infarction, stroke, or revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting

3.2. Secondary endpoints

Secondary endpoints	Secondary endpoint variables
Clinical adverse events	- Newly diagnosed DM after study enrollment - Hospitalization due to heart failure - Deep vein thrombosis or Pulmonary thromboembolism - Percutaneous trans-luminal angioplasty on peripheral artery obstructive disease - Aortic intervention or operation - ESRD - The rate of statin treatment discontinuation
Laboratory abnormality	- Aminotransferase elevation: (ALT > 3 x ULN) - Creatine kinase elevation: (CK>5 x ULN) - Increase of creatinine (>50% from baseline)

4. METHODS and DESIGN

This study is designed as a prospective randomized study in order to compare clinical outcomes of the targeted statin group versus the non-targeted high-intensity statin group in patients with coronary artery disease as a high ASCVD risk group.

4.1. Patient enrollment

4.1.1. Inclusion criteria

- Patients ≥19 years old.
- Patients clinically diagnosed with coronary artery disease including stable angina, unstable angina, acute non-ST elevation myocardial infarction and acute ST elevation myocardial infarction.
- Patients with signed informed consent.

4.1.2. Exclusion criteria

- Pregnant women or women with potential childbearing.
- Patients with severe adverse events or hypersensitive to statin.
- Patients receiving drug that have a drug interaction with statin (strong inhibitor of cytochrome p-450 3A4 or 2C9).
- Life expectancy <3 years.
- Severe hepatic dysfunction (3 times normal reference values).

4.2. Sample Size and Statistical Analyses

4.2.1. Determination of sample size

Our primary hypothesis is that the targeted statin therapy group would be non-inferior to the non-targeted high-intensity statin therapy group in the patients with coronary artery disease as a high risk ASCVD patients in terms of long-term clinical outcomes as an intention-to-treat population.

On the basis of a previous study, we expected about 4% incidence of MACCE per year in both groups (18). Therefore, total expected MACCE rate was estimated as 12% for 3-year observation. A non-inferiority margin of 3.0% is selected. With a one-sided type 1 error of 2.5%, power of 80%, and 15% follow-up loss, a sample size of 4336 patients (consisted of 2168

patients for each group) is required, and final study population will include 4400 patients.

4.2.2. Statistical Analyses

For the primary objective, *it will be tested whether the targeted statin therapy group would be non-inferior* to non-targeted high-intensity statin therapy group in terms of primary endpoint in the intention-to-treat population. Cumulative event rate during the clinical follow-up will be estimated using the Kaplan-Meier method. A 95% confidence interval of the difference in event rates will be calculated. If the upper limit of the 97.5% confidence interval of the differences in the two groups is less than 3.0% of a non-inferiority margin, it will be declared that the targeted statin therapy group is non-inferior to the non-targeted high-intensity statin therapy group. As a sensitivity analysis, analysis of the primary endpoint also will be performed on the per-protocol population. Intention-to-treat population will include all randomized patients and they will be compared according to the assigned group regardless of the treatment they actually given. In the per-protocol population, the following patients with protocol deviations will be excluded; 1) patients found to be ineligible, 2) informed consent not obtained, or 3) randomized therapy (assigned therapy) not implemented (a total period of the discontinued the allocated treatment >5% of a total follow-up period or statin intensity non-adjustment according to the follow-up LDL-C level).

Data will be expressed as mean ± SD or number (percent). Comparisons of proportions will be made using the Chi-square method. Continuous variables will be compared with the student's t-test. If the distribution is skewed, a non-parametric test will be used.

5. STUDY PROCEDURE

All eligible patients who have clinical ASCVD including CAD, DM or dyslipidemia (LDL-C >190 mg/dl) assessed by medical record review will be screened and enrolled according to inclusion/exclusion criteria after voluntary agreement with informed consent. At the time enrollment, a randomization will be performed with a stratification of baseline LDL-C level, presence of diabetes mellitus, and acute coronary syndrome; targeted statin therapy group or non-targeted high-intensity therapy group as a 1:1 ratio.

Patients allocated to targeted statin therapy group will be received statin therapy with

dose (intensity) adjustment according to the LDL-C level with a decision of the physicians. Statin intensity will be increased or decreased to according to the target LDL-C goal (lower than 70 mg/dL) at scheduled sequential laboratory follow–up. Patients allocated to non-targeted high-intensity statin group will be received high-intensity statin according to 2013 ACC/AHA guideline. Thus, the patients allocated to non-targeted high-intensity statin therapy group will receive high-intensity statin, irrespectively baseline LDL-C level.

Baseline characteristics, laboratory findings including lipid profiles will be obtained at enrollment. Clinical check-up with laboratory exam including lipid profile will be followed at 6 weeks, 3 months, and 6 months until 12months after enrollment. After 12 months from enrollment, we will follow clinical check-up and laboratory evaluation will be conducted every 1 year for 2 years.

5.1. Estimated the 10-year ASCVD risk

The 10-year ASCVD risk should be estimated using the Pooled Cohort Equations developed by the Risk Assessment Work Group to estimate the 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke) for the identification of candidates for statin therapy. These equations should be used to predict stroke as well as CHD events in non-Hispanic Caucasian and African American. For other ethnic groups, Guideline recommend use of the equations for non-Hispanic whites. Diabetes mellitus patients with LDL-C >190mg/dl are enrolled without calculating 10-year ASCVD risk as a high risk.

The information required to estimate ASCVD risk included age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes mellitus, and smoking status.

5.2. Statin Therapy

Patients will receive statin therapy according to statin intensity. Statin intensity is defined as classification of statin intensity provided by 2013 ACC/AHA guideline as follows;

High-intensity Statin Therapy	**Moderate-intensity Statin Therapy**
Daily dose lowers LDL-C on average, by approximately ≥ 50%	Daily dose lowers LDL-C on average, by approximately 30% to <50%

Atorvastatin (40)–80 mg **Rosuvastatin 20 (40) mg**	**Atorvastatin 10 (20) mg** **Rosuvastatin (5) 10 mg**

5.2.1. Targeted statin therapy group

5.2.1.1. Initial statin treatment

(1) Statin naïve patients:

- Patients will be received moderate intensity statin therapy (atorvastatin 20 mg or rosuvastatin 10 mg).

(2) Patients already received statin therapy:

- Baseline LDL-C <70 mg/dL: maintain the statin intensity at enrollment.
  - Ex) If the patients were taking low-intensity statin, atorvastatin 10 mg or rosuvastatin 5mg will be given.
  - Ex) If the patients were taking moderate-intensity statin therapy, atorvastatin 20 mg or rosuvastatin 10 mg will be given.
  - Ex) If the patients were taking high-intensity statin therapy, atorvastatin 40 mg or rosuvastatin 20 mg will be given.
- Baseline LDL-C ≥70 mg/dL: Start with higher-intensity statin than taking at enrollment.
  - Ex) If the patients were taking low-intensity statin therapy, atorvastatin 20mg or rosuvastatin 10 mg will be given.
  - Ex) If the patients were taking moderate/high-intensity statin therapy, atorvastatin 40mg or rosuvastatin 20mg will be given.

5.2.1.2. Titration guided by follow-up LDL-C levels

- Follow-up LDL-C <50 mg/dL: down-titrate statin intensity
- 50 mg/dL ≤ Follow-up LDL-C <70 mg/dL: maintain current statin
- Follow-up LDL-C ≥70 mg/dL: up-titrate statin intensity

5.2.2. Non-targeted high-intensity statin therapy group

- Patients assigned to the non-targeted high-intensity statin group will be received high-intensity statin therapy (atorvastatin 40mg or rosuvastatin 20mg) regardless of their baseline LDL-C levels.
- Patients assigned to the non-targeted high-intensity statin group will be maintained the

high-intensity statin therapy regardless of their follow-up LDL-C levels (ex. Maintain high-intensity statin if LDL-C <40 mg/dL).

5.3 Randomization

Patients will be randomized to receive either of targeted LDL-C statin therapy group or non-targeted high-intensity statin therapy group in a 1:1 ratio. Randomization will be stratified according to baseline LDL-C, presence of diabetes mellitus, and acute coronary syndrome. Also, patients will be randomized in a ratio of 1:1 according to the two different types of lipid-lowering treatment (atorvastatin or rosuvastatin).

5.4. Follow-Up

All patients will be followed-up clinically, and will be received dietary counseling at 30 days and 6 months. At 6 weeks, 3 months, and 6 months until 12months after enrollment, patients will be visited to the out-patient clinic with laboratory test until the first year (Target LDL-C goal: less than 70 mg in the targeted statin therapy group).

After first year, patients were visited every 1 year with clinical follow-up and blood test. Blood samples were obtained at randomization, at 6weeks, 3, 6, 12, 24, 36 months with clinical follow-up.

Table 1. Patients Schedule for clinical and laboratory follow-up

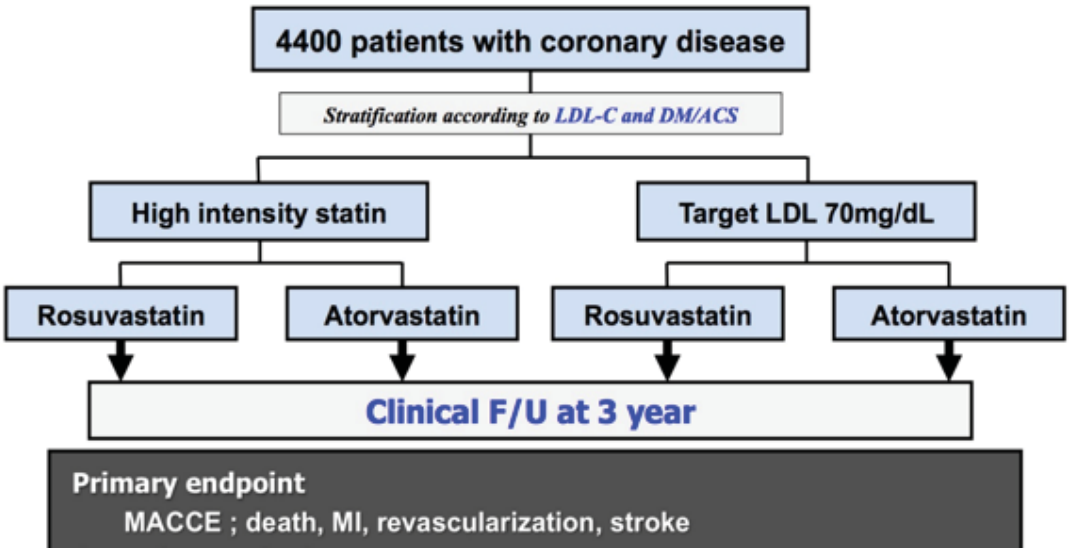
Measurement	Baseline	6 W ± 2 W	Follow-up				
			3 M ± 1 M	6 M ± 1 M	12 M ± 2 M	24 M ± 2 M	36 M ± 2 M
Informed consent	O						
Inclusion/Exclusion criteria	O						
Clinical/Medical history	O						
Vital Status & Physical exam	O	O	O	O	O	O	O
Weight & Height	O		O	O	O	O	O
Waist	O				O	O	O
ECG (12 lead)	O				O	O	O
CBC, Routine chemistry, Lipid profile, Creatine	O	O (Lipid	O (Lipid	O (Lipid	O	O	O

kinase (CK), hs-CRP		profile, AST/ALT, CK only)	profile, AST/ALT, CK only, and optional)	profile, AST/ALT, CK only, and optional)			
HbA1C	O				O	O	O
Pregnancy test (if applicable)	O						
Current Medication	O	O	O	O	O	O	O
Serious Adverse Events	O	O	O	O	O	O	O

5.5. General guidelines for concomitant treatment

- Risk factor modification should be initiated for all patients as recommended.
- All medication including dual antiplatelet treatment except statin will be used according to current guidelines.

6. STUDY ALGORITHM



7. STUDY QUALITY MAMAGEMENT

7.1 Ethical issue

The primary investigator (PI) has the responsibility to abide by ethical requirements related to this study. This study will be conducted with approval of institutional review board (IRB) and after voluntary agreements with informed consent from all patients. In addition, we disclose that this study is not contrary to Helsinki declaration and ICH/GCP.

7.2 Data and safety monitoring

The Principal Investigator (PI) will be responsible for ensuring participants' safety. The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

Data Safety Monitoring Board	Severance Hospital, Seoul	Sang Hak Lee, MD Geu-Ru Hong, MD Jae Sun Uhm, MD

7.3. Frequency of data and safety monitoring

The PI will be informed of serious adverse events as soon as they occur and will notify the DSMB within 24 hours of notification. DSMB will meet twice annually, either in-person or by teleconference call to review study progress, data quality, and participant safety.

7.4 Content of data and safety monitoring report

The content of the data and safety monitoring report will include study status, participant descriptive information, safety information, and study quality.

7.5 Informed consent

The Principal Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided. The Principal Investigator must store the original, signed Informed Consent Form.

8. DEFINITIONS

Enrolled Patient

The point of enrollment occurs when a patient or patient's legally authorized representative has provided written informed consent to participate in the trial

Principal Investigator

A physician-specialist responsible for overseeing trial conduct at all sites, protocol compliance, and relevant KFDA regulations

Primary Investigator

A physician responsible for conducting the study at each investigational site

MACCE (Major Adverse Cardiac and Cerebrovascular Event)

Defined as composite of death, MI, revascularization, and stroke

Death

All death will be categorized as cardiac death and non-cardiac death according to the following definition: Cardiac death is defined as death due to myocardial infarction, cardiac perforation or tamponade, arrhythmia, stroke within 30 days of the procedure or related to the procedure, death due to a complication of the procedure, and any death in which a cardiac cause cannot be excluded, as adjudicated by blinded clinical events committee.

Myocardial Infarction (MI)

Myocardial Infarction Classification and Criteria for Diagnosis is defined by the Academic Research Consortium as follows: Spontaneous myocardial infarction based on clinical symptoms, electrocardiographic changes, or abnormal findings during imaging studies, combined with an increase in the creatine kinase myocardial band fraction above the upper normal limit or an increase in troponin-T or troponin-I level >99th percentile of the upper normal limit.

Revascularization

Revascularization is defined by the Academic Research Consortium as follows: All revascularizations will be classified as clinically indicated* or not clinically indicated by the investigator prior to angiography. *Clinically indicated revascularization: A revascularization is considered clinically indicated if angiography shows a percent diameter stenosis ≥ 50% and if one of the following occurs: (1) A positive history of recurrent angina pectoris, presumably related to the target vessel; (2) Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; (3) Abnormal results of any invasive functional diagnostic test (eg, Doppler flow velocity reserve, fractional flow reserve); (4) A revascularization with a diameter stenosis ≥ 70% even in the absence of the above-mentioned ischemic signs or symptoms.

Stroke

Stroke was defined as a sudden focal neurologic deficit of presumed cerebrovascular etiology that persisted beyond 24 hours and was not due to another identifiable cause. An event matching this definition but lasting less than 24hours was considered to be a transient ischemic attack. Brain imaging (computed tomography o magnetic resonance imaging) was recommended for all suspected strokes.

New onset diabetes mellitus

New-onset diabetes mellitus was defined as initiating antidiabetes medication according to annual medication inventories or fasting plasma glucose > 125mg/dl. Once an individual was defined as having diabetes by either criterion, they were considered to have diabetes throughout follow-up.

Deep vein thrombosis

Deep vein thrombosis was defined as a positive duplex ultrasound or venogram or computed tomography.

Pulmonary thromboembolism

Pulmonary thromboembolism was determined using results of computed tomography, ventilation/perfusion scan, or angiography. thrombosis events were classified as idiopathic or

secondary (occurring within 90 days of major trauma, surgery, or marked immobility or associated with active cancer or chemotherapy)

Percutaneous trans-luminal angioplasty on peripheral artery obstructive disease

Percutaneous trans-luminal angioplasty on peripheral artery obstructive disease was defined as recanalization of pelvic and leg arteries in patients with intermittent claudication, rest pain, and /or ischemic ulceration, in addition to stenosis, total occlusions can be recanalized.

Aortic intervention or operation

Surgical or interventional repair of aortic dilatation or dissection.

ESRD

It was not included temporary renal replacement therapy due to acute renal failure associated with other clinical situation.

Aminotransferase elevation:

Definition of Aminotransferase elevation was Aminotransferase increase from baseline and > 3 x ULN (upper limit of normal).

Creatinine kinase elevation:

Definition of Creatine kinase elevation was Creatine kinase increase from baseline and > 5 x ULN (upper limit of normal).

Muscle associated adverse events:

Muscle-associated AEs as myalgia, muscle spam, muscle weakness, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, arthralgia, rhabdomyolysis

Increase of creatinine:

Definition of creatinine increase was creatinine 50% increase from baseline and > ULN (upper limit of normal).

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2. Last version (11 August 2022) of the LODESTAR protocol

Low-density lipoprotein cholesterol-targeting statin therapy versus intensity-based statin therapy in patients with coronary artery disease: a randomized comparison trial

[LODESTAR trial]

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Version 6.5 (August 11, 2022)

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Protocol

1. Protocol Summary

Title of Study	Low-density lipoprotein cholesterol-targeting statin therapy versus the intensity-based statin therapy in patients with coronary artery disease: a randomized comparison trial [LODESTAR Trial]
Study Centers	Division of Cardiology, Yonsei Cardiovascular Hospital, Yonsei University College of Medicine
Phase of Development	Phase IV
Objective	To compare clinical safety & efficacy of targeting LDL-C level <70 mg/dL statin therapy (statin therapy with target group; according to 2013 ACC/AHA guideline) versus non-targeting LDL-C level high-intensity statin therapy (high-intensity statin therapy without target group) in patients with coronary artery disease for secondary prevention.
Methodology	Prospective, open label, randomized study
Number of Subjects	Total 4400 patients with coronary artery disease patients requiring statin treatment
Study Design	• Prospective, open label, randomized, multicenter study • Randomization with a 1:1 to either of statin therapy with target group or high-intensity statin therapy without target group • Randomized stratification according to baseline LDL-C, presence of diabetes mellitus, and acute coronary syndrome • Additional allocation to rosuvastatin or atorvastatin within each group • Clinical follow-up for 36 months
Diagnosis and Main Criteria for Inclusion	• Patients ≥ 19 years old • Patients clinically diagnosed with coronary artery disease including stable angina, unstable angina, acute non-ST elevation myocardial infarction and acute ST elevation myocardial infarction • Patients with signed informed consent
Primary and Major Secondary Endpoints	• **Primary endpoint:** Major Adverse Cardiac and Cerebrovascular Event (MACCE); Clinical outcomes composed of death from any cause, myocardial infarction, stroke, and revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting • **Secondary endpoint:**

	1. New onset diabetes mellitus after randomization 2. Hospitalization due to heart failure 3. Deep vein thrombosis or pulmonary thromboembolism 4. Percutaneous trans-luminal angioplasty on peripheral artery obstructive disease 5. Aortic intervention or operation 6. End-stage renal disease 7. The rate of statin treatment discontinuation 8. Cataract operation 9. Composite of laboratory abnormality: - Aminotransferase elevation: (ALT > 3 x ULN) - Creatine kinase elevation: (CK>5 x ULN) - Increase of creatinine
Statistical Methods	Clinical outcome (MACCE) and adverse events - Cumulative incidence using Kaplan-Meier method - Log-rank test - Cox proportional hazard regression model
Study Duration	Patient enrollment: September 19, 2015 ~ March 31, 2021 Follow-up duration: 3 years Total duration of the study: September 19, 2015 ~ March 31, 2024
Participating Sites	1. Yonsei University Severance Hospital 2. Gangnam Severance Hospital 3. Inje University Ilsan Paik Hospital 4. Myong Ji Hospital 5. Gachon University Gil medical Center 6. Jeju national University Hospital 7. Kangbuk Samsung Hospital 8. Inje University Busan Paik Hospital 9. Wonju Severance Christian Hospital 10. Chosun University Hospital 11. Keimyung University Dongsan Medical Center 12. Daegu Catholic University Medical Center

2. BACKGROUND

Almost one-third of the population will die as a result of heart attack or stroke associated with atherosclerotic cardiovascular disease (ASCVD), the leading cause of death and disability today (1). The major treatable causes of ASCVD include hypercholesterolemia, hypertension, diabetes, and an unhealthy lifestyle. Over the past 3 decades, on the basis of observational studies and some randomized controlled trials (RCTs), guideline recommendations have been developed focusing on treatment strategies to reduce these risk factors. Because low-density lipoprotein (LDL) plays a significant role in the promotion, development, and progression of vascular atherosclerosis, a primary strategy in these efforts has been lowering of LDL cholesterol in at-risk populations (2). Hydroxymethylglutaryl-CoA reductase inhibitor, statin, has beneficial properties include atherosclerotic plaque stabilization, oxidative stress reduction, enhancement of endothelial function and a decrease in vascular inflammation beyond their lipid-lowering effect (3). In various clinical trials, statins have shown clinical benefits in primary and secondary prevention (4-6). Epidemiological studies demonstrate a continuous relationship between cholesterol levels and ASCVD risk, from low to high (7). RCTs show the reverse: the more LDL-C is lowered, the greater the risk reduction (8, 9). Furthermore, there appears to be no limit beneath which a lower LDL-C fails to reduce risk. Meta-analysis of statin trials show that risk reduction extends into the very low range for LDL-C (10). Thus, it can be said that “the lower, the better” is true for cholesterol reduction.

The NCEP ATP III guideline and 2004 update have served as the standard of care for at-risk patients with hyperlipidemia for nearly a decade (11). Guideline focused on the fasting lipid panel as the initial evaluation of lipid-related CVD risk. Within each category of ASCVD risk, targets of treatment are then specified in these recommendations. In the ATP III guidelines, cardiovascular disease (CVD) and diabetes mellitus (DM) as a coronary heart disease (CHD) risk equivalent were considered as high-risk category. LDL-C was considered the primary target of therapy and an optional goal of LDL-C < 70mg/dl in these high–risk patients. The European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines for the management of dyslipidemias define documented cardiovascular disease, previous myocardial infarction, coronary revascularization, ischemic stroke, DM with target organ damage, or moderate to severe CKD as very high-risk group and recommended target LDL -C level of <70mg/dL and/or ≥50% LDL-C reduction when target level cannot reach (12).

To update previous guideline recommendations, the 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adult was recently issued (13). For processing this new guideline, it was unable to find RCT evidence to support continued use of specific LDL-C and/or non-HDL-C targets. In other words, use of LDL-C targets may result in under-treatment with evidence-based statin therapy or overtreatment with non-statin drugs that have not been shown to reduce ASCVD events in RCT. On the basis of evidence, 4 major statin benefit groups were identified: 1) with clinical ASCVD, 2) primary elevations of LDL-C≥190mg/dL, 3) diabetes age 40-75 years with LDL-C 70-189 and without clinical ASCVD, or 4) estimated 10-year ASCVD risk ≥7.5% by new Pooled Cohort Equations. For these groups, the new guideline proposes that implementation of cholesterol-lowering treatment using evidenced-based intensity of statin therapy should be treated in patients without such targets.

There are several concerns about using fixed-high potent statin following new guideline, especially for Asian population. First, statin potency from recent issued guideline was set from the studies composed of mainly Caucasian population (14). In addition, there was an inconsistency of efficacy of statin according to ethnic population. Asian population showed more profound LDL reduction not only from high potent statin but from moderate to low potent statin (15). Second, there is increased risk of adverse effects on high intensity statin therapy. For example, statin therapy modestly increases the risk for developing type 2 diabetes. The risk is lower for moderate-intensity statins (approximately 0.1 excess case of diabetes per 100 statin-treated patients/year) than for high-intensity statins (approximately 0.3 excess case of diabetes per 100 statin-treated patients/year) (16, 17).

It is no surprise that a revolutionary change from decades of emphasis on LDL-C goals of therapy in dyslipidemia would generate considerable controversy and confusion. These were due to substantive differences in both the process of guideline development and the content of the new ACC/AHA clinical practice recommendations. The 2013 ACC/AHA Guidelines are narrower in scope and consider 3 critical questions in lipid management for ASCVD prevention. They provide discussion of evidence but limited recommendations for the treatment of special populations (e.g., age <40 to >75 years; Asian ethnic populations) and management of patients with complex dyslipidemias, suboptimal response to therapy, adverse effects on statin therapy, or complete statin intolerance.

There are these limitations according to the guidelines and there is no direct data from RCTs that compare the efficacy of the targeted LDL-C statin therapy and the non-targeted high-intensity statin therapy until now. Therefore, we will evaluate the clinical validity of the targeted LDL-C level (< 70 mg/dl) statin therapy for secondary prevention of ASCVD compared with the non-targeted LDL-C level high-intensity statin therapy in this study.

3. STUDY OBJECTIVES

The purpose of this study is to compare clinical efficacy and safety of targeting LDL-C level <70 mg/dL statin therapy (targeted statin group) *versus* non-targeting LDL-C level high-intensity statin therapy (non-targeted high-intensity statin group) in patients with coronary artery disease as a high ASCVD risk group.

3.1. Primary endpoint

Primary endpoint	Primary endpoint variable
Major Adverse Cardiac and Cerebrovascular Event (MACCE)	Clinical outcomes composed of death from any cause, myocardial infarction, stroke, or revascularization with either percutaneous coronary intervention or coronary-artery bypass grafting

3.2. Secondary endpoints

Secondary endpoints	Secondary endpoint variables
Clinical adverse events	- Newly diagnosed DM after study enrollment - Hospitalization due to heart failure - Deep vein thrombosis or Pulmonary thromboembolism - Percutaneous trans-luminal angioplasty on peripheral artery obstructive disease - Aortic intervention or operation - ESRD - The rate of statin treatment discontinuation - Cataract operation
Laboratory abnormality	- Aminotransferase elevation: (ALT > 3 xULN) - Creatine kinase elevation: (CK>5 xULN)

	- Increase of creatinine (>50% from baseline)

4. METHODS and DESIGN

This study is designed as a prospective randomized study in order to compare clinical outcomes of the targeted statin group versus the non-targeted high-intensity statin group in patients with coronary artery disease as a high ASCVD risk group.

4.1. Patient enrollment

4.1.1. Inclusion criteria

- Patients ≥19 years old.
- Patients clinically diagnosed with coronary artery disease including stable angina, unstable angina, acute non-ST elevation myocardial infarction and acute ST elevation myocardial infarction.
- Patients with signed informed consent.

4.1.2. Exclusion criteria

- Pregnant women or women with potential childbearing during the study period.
- Patients with severe adverse events or hypersensitive to statin.
- Patients receiving drug that have a drug interaction with statin (strong inhibitor of cytochrome p-450 3A4 or 2C9).
- Patients with risk factors for myopathy; hereditary muscle disorder, hypothyroidism, alcohol use disorder, severe hepatic dysfunction (3 times normal reference values) or rhabdomyolysis.
- Life expectancy <3 years.
- Patient with who cannot be followed up for more than 1 year.
- Patients who cannot understand the consent form.

4.2. Sample Size and Statistical Analyses Plan

4.2.1. Determination of sample size

Our primary hypothesis is that the targeted statin therapy group would be non-inferior to the non-targeted high-intensity statin therapy group in the patients with coronary artery disease

as a high risk ASCVD patients in terms of long-term clinical outcomes as an intention-to-treat population.

On the basis of a previous study, we expected about 4% incidence of MACCE per year in both groups (18). Therefore, total expected MACCE rate was estimated as 12% for 3-year observation. A non-inferiority margin of 3.0% is selected. With a one-sided type 1 error of 2.5%, power of 80%, and 15% follow-up loss, a sample size of 4336 patients (consisted of 2168 patients for each group) is required, and final study population will include 4400 patients.

4.2.2. Statistical Analyses

For the primary objective, *it will be tested whether the targeted statin therapy group would be non-inferior* to non-targeted high-intensity statin therapy group in terms of primary endpoint in the intention-to-treat population. Cumulative event rate during the clinical follow-up will be estimated using the Kaplan-Meier method. A 95% confidence interval of the difference in event rates will be calculated. If the upper limit of the 97.5% confidence interval of the differences in the two groups is less than 3.0% of a non-inferiority margin, it will be declared that the targeted statin therapy group is non-inferior to the non-targeted high-intensity statin therapy group. As a sensitivity analysis, analysis of the primary endpoint also will be performed on the per-protocol population. Intention-to-treat population will include all randomized patients and they will be compared according to the assigned group regardless of the treatment they actually given. In the per-protocol population, the following patients with protocol deviations will be excluded; 1) patients found to be ineligible, 2) informed consent not obtained, or 3) randomized therapy (assigned therapy) not implemented (a total period of the discontinued the allocated treatment >5% of a total follow-up period or statin intensity non-adjustment according to the follow-up LDL-C level).

For secondary endpoints, the incidence or cumulative incidences of each endpoint using a Kaplan-Meier plot will be calculated for comparisons.

Missing variables will not be imputed for planned analyses, except where otherwise specified. The patient with the missing values will be excluded from the variable-related analysis but included in the analysis not related to the missing variable. For the study endpoints, patients lost to follow-up and subsequently lost to assessment of primary endpoint, will be considered to be censored in the estimation of Kaplan-Meier event rates.

Subgroup analysis will be made to compare the HR of experimental arm against control arm stratified by prespecified subgroups; age (<65 vs. ≥65 years), sex (male vs. female), body mass index (<25 vs. ≥25 kg/m^2), diabetes (Yes vs. No), hypertension (Yes vs. No), chronic kidney disease (Yes vs. No), clinical presentation (angina vs. NSTEMI/STEMI), and baseline LDL-C level (<100 vs. ≥100 mg/dL).

Demographic and clinical characteristics will be presented to confirm that there is no difference between each administration group by comparing the characteristics of clinical subjects in the treatment group and the control group before enrollment in the clinical trial. Demographic information such as gender and age will be evaluated in intention to treat manner.

Data will be expressed as mean ± SD or number (percent). Comparisons of proportions will be made using the Chi-square method. Continuous variables will be compared with the student's t-test. If the distribution is skewed, a non-parametric test will be used.

5. STUDY PROCEDURE

All eligible patients who have clinical ASCVD including CAD, DM or dyslipidemia (LDL-C >190 mg/dL) assessed by medical record review will be screened and enrolled according to inclusion/exclusion criteria after voluntary agreement with informed consent. At the time enrollment, a randomization will be performed with a stratification of baseline LDL-C level, presence of diabetes mellitus, and acute coronary syndrome; targeted statin therapy group or non-targeted high-intensity therapy group as a 1:1 ratio.

Patients allocated to targeted statin therapy group will be received statin therapy with dose (intensity) adjustment according to the LDL-C level with a decision of the physicians. Statin intensity will be increased or decreased to according to the target LDL-C goal (lower than 70 mg/dL) at scheduled sequential laboratory follow–up. Patients allocated to non-targeted high-intensity statin group will be received high-intensity statin according to 2013 ACC/AHA guideline. Thus, the patients allocated to non-targeted high-intensity statin therapy group will receive high-intensity statin, irrespectively baseline LDL-C level.

Baseline characteristics, laboratory findings including lipid profiles will be obtained at enrollment. Clinical check-up with laboratory exam including lipid profile will be followed at 6

weeks, 3 months, and 6 months until 12months after enrollment. After 12 months from enrollment, we will follow clinical check-up and laboratory evaluation will be conducted every 1 year for 2 years.

5.1. Estimated the 10-year ASCVD risk

The 10-year ASCVD risk should be estimated using the Pooled Cohort Equations developed by the Risk Assessment Work Group to estimate the 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke) for the identification of candidates for statin therapy. These equations should be used to predict stroke as well as CHD events in non-Hispanic Caucasian and African American. For other ethnic groups, Guideline recommend use of the equations for non-Hispanic whites. Diabetes mellitus patients with LDL-C >190mg/dl are enrolled without calculating 10-year ASCVD risk as a high risk.

The information required to estimate ASCVD risk included age, sex, race, total cholesterol, HDL cholesterol, systolic blood pressure, blood pressure lowering medication use, diabetes mellitus, and smoking status.

5.2. Statin Therapy

Patients will receive statin therapy according to statin intensity. Statin intensity is defined as classification of statin intensity provided by 2013 ACC/AHA guideline as follows;

High-intensity Statin Therapy	**Moderate-intensity Statin Therapy**
Daily dose lowers LDL-C on average, by approximately ≥ 50%	Daily dose lowers LDL-C on average, by approximately 30% to <50%
Atorvastatin (40)–80 mg **Rosuvastatin 20 (40) mg**	**Atorvastatin 10 (20) mg** **Rosuvastatin (5) 10 mg**

5.2.1. Targeted statin therapy group

5.2.1.1. Initial statin treatment

(1) Statin naïve patients:

- Patients will be received moderate intensity statin therapy (atorvastatin 20 mg or rosuvastatin 10 mg).

(2) Patients already received statin therapy:

- Baseline LDL-C <70 mg/dL: maintain the statin intensity at enrollment.
  - Ex) If the patients were taking low-intensity statin, atorvastatin 10 mg or rosuvastatin 5mg will be given.
  - Ex) If the patients were taking moderate-intensity statin therapy, atorvastatin 20 mg or rosuvastatin 10 mg will be given.
  - Ex) If the patients were taking high-intensity statin therapy, atorvastatin 40 mg or rosuvastatin 20 mg will be given.
- Baseline LDL-C ≥70 mg/dL: Start with higher-intensity statin than taking at enrollment.
  - Ex) If the patients were taking low-intensity statin therapy, atorvastatin 20mg or rosuvastatin 10 mg will be given.
  - Ex) If the patients were taking moderate/high-intensity statin therapy, atorvastatin 40mg or rosuvastatin 20mg will be given.

5.2.1.2. Titration guided by follow-up LDL-C levels

- Follow-up LDL-C <50 mg/dL: down-titrate statin intensity
- 50 mg/dL ≤ Follow-up LDL-C <70 mg/dL: maintain current statin
- Follow-up LDL-C ≥70 mg/dL: up-titrate statin intensity

5.2.2. Non-targeted high-intensity statin therapy group

- Patients assigned to the non-targeted high-intensity statin group will be received high-intensity statin therapy (atorvastatin 40mg or rosuvastatin 20mg) regardless of their baseline LDL-C levels.
- Patients assigned to the non-targeted high-intensity statin group will be maintained the high-intensity statin therapy regardless of their follow-up LDL-C levels (ex. Maintain high-intensity statin if LDL-C <40 mg/dL).

5.3 Randomization

Patients will be randomized to receive either of targeted LDL-C statin therapy group or non-targeted high-intensity statin therapy group in a 1:1 ratio. Randomization will be stratified according to baseline LDL-C, presence of diabetes mellitus, and acute coronary syndrome. Also, patients will be randomized in a ratio of 1:1 according to the two different types of lipid-lowering treatment (atorvastatin or rosuvastatin).

5.4. Follow-Up

All patients will be followed-up clinically, and will be received dietary counseling at 30 days and 6 months. At 6 weeks, 3 months, and 6 months until 12months after enrollment, patients will be visited to the out-patient clinic with laboratory test until the first year (Target LDL-C goal: less than 70 mg in the targeted statin therapy group).

After first year, patients were visited every 1 year with clinical follow-up and blood test. Blood samples were obtained at randomization, at 6weeks, 3, 6, 12, 24, 36 months with clinical follow-up.

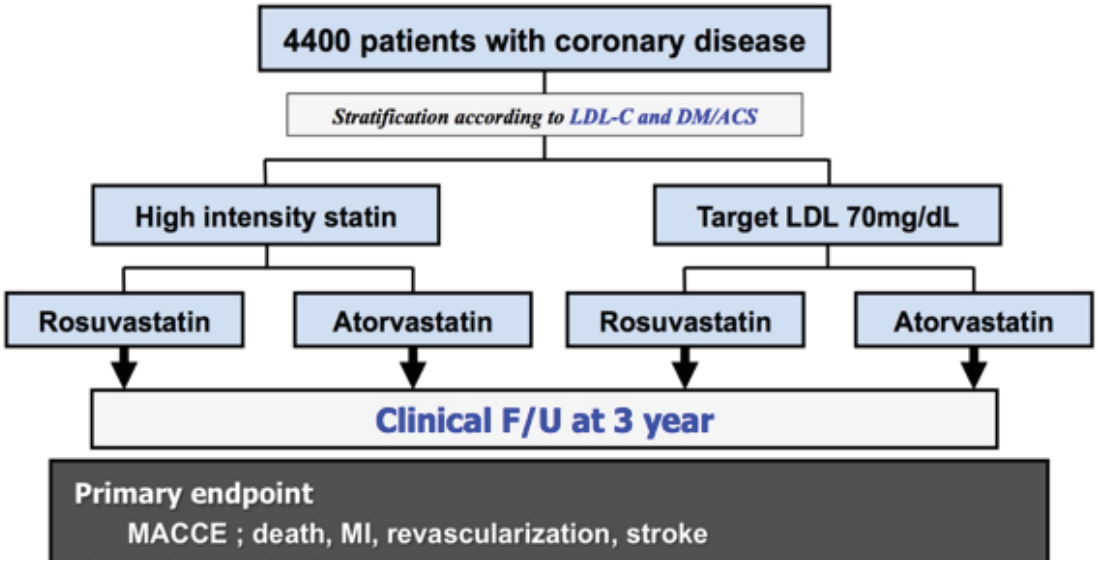
Table 1. Patients Schedule for clinical and laboratory follow-up

Measurement	Baseline	6 W ± 2 W	Follow-up				
			3 M ± 1 M	6 M ± 1 M	12 M ± 2 M	24 M ± 2 M	36 M ± 2 M
Informed consent	O						
Inclusion/Exclusion criteria	O						
Clinical/Medical history	O						
Vital Status & Physical exam	O	O	O	O	O	O	O
Weight & Height	O		O	O	O	O	O
Waist	O				O	O	O
ECG (12 lead)	O				O	O	O
CBC, Routine chemistry, Lipid profile, Creatine kinase (CK), hs-CRP	O	O (Lipid profile, AST/ALT, CK only)	O (Lipid profile, AST/ALT, CK only, and optional)	O (Lipid profile, AST/ALT, CK only, and optional)	O	O	O
HbA1C	O				O	O	O
Pregnancy test (if applicable)	O						
Current Medication	O	O	O	O	O	O	O
Serious Adverse Events	O	O	O	O	O	O	O

5.5. General guidelines for concomitant treatment

- Risk factor modification should be initiated for all patients as recommended.
- All medication including dual antiplatelet treatment except statin will be used according to current guidelines.

6. STUDY ALGORITHM



7. STUDY QUALITY MAMAGEMENT

7.1 Ethical issue

The primary investigator (PI) has the responsibility to abide by ethical requirements related to this study. This study will be conducted with approval of institutional review board (IRB) and after voluntary agreements with informed consent from all patients. In addition, we disclose that this study is not contrary to Helsinki declaration and ICH/GCP.

7.2 Data and safety monitoring

The Principal Investigator (PI) will be responsible for ensuring participants' safety. The Data and Safety Monitoring Board (DSMB) will act in an advisory capacity to monitor participant safety, evaluate the progress of the study, to review procedures for maintaining the confidentiality of data, the quality of data collection, management, and analyses.

Data Safety Monitoring Board	Yongin Severance Hospital Ewha Womans Mokdong Hospital, Seoul Chung-Ang University Hospital, Seoul Severance Hospital, Seoul	Jae Sun Uhm, MD Junbeom Park, MD Iksung Cho, MD Dong-Ho Shin, MD

7.3. Frequency of data and safety monitoring

The PI will be informed of serious adverse events as soon as they occur and will notify the DSMB within 24 hours of notification. DSMB will meet twice annually, either in-person or by teleconference call to review study progress, data quality, and participant safety.

7.4 Content of data and safety monitoring report

The content of the data and safety monitoring report will include study status, participant descriptive information, safety information, and study quality.

7.5 Informed consent

The Principal Investigator will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient should be given the opportunity to ask questions and allowed time to consider the information provided. The Principal Investigator must store the original, signed Informed Consent Form.

7.6. Clinical event adjudication

The Clinical Events Adjudication Committee (CEAC) is comprised of interventional and non-interventional cardiologists who are not participants in the study. The CEAC is charged with the development of specific criteria used for the categorization of clinical events and clinical endpoints in the study which are based on protocol. At the onset of the trial, the CEAC will establish explicit rules outlining the minimum amount of date required, and the algorithm followed in order to classify a clinical event. All members of the CEAC will be blinded to the primary results of the trial.

The CEAC will meet regularly to review and adjudicate all clinical events. The

Committee will also review and rule on all deaths that occur throughout the trial.

Clinical Event Committee	Severance Cardiovascular Hospital, Seoul Kyung Hee University Hospital Kwan Dong University Hospital Ehwa Women's University Seoul Hospital	Sang Hak Lee, MD (Chair) Jung-Myung Lee, MD Hyoung-Bok Park, MD Choongki Kim, MD

8. DEFINITIONS

Enrolled Patient

The point of enrollment occurs when a patient or patient's legally authorized representative has provided written informed consent to participate in the trial

Principal Investigator

A physician-specialist responsible for overseeing trial conduct at all sites, protocol compliance, and relevant KFDA regulations

Primary Investigator

A physician responsible for conducting the study at each investigational site

MACCE (Major Adverse Cardiac and Cerebrovascular Event)

Defined as composite of death, MI, revascularization, and stroke

Death

All death will be categorized as cardiac death and non-cardiac death according to the following definition: Cardiac death is defined as death due to myocardial infarction, cardiac perforation or tamponade, arrhythmia, stroke within 30 days of the procedure or related to the procedure, death due to a complication of the procedure, and any death in which a cardiac cause cannot be excluded, as adjudicated by blinded clinical events committee.

Myocardial Infarction (MI)

Myocardial Infarction Classification and Criteria for Diagnosis is defined by the Academic Research Consortium as follows: Spontaneous myocardial infarction based on clinical

symptoms, electrocardiographic changes, or abnormal findings during imaging studies, combined with an increase in the creatine kinase myocardial band fraction above the upper normal limit or an increase in troponin-T or troponin-I level >99th percentile of the upper normal limit.

Revascularization

Revascularization is defined by the Academic Research Consortium as follows: All revascularizations will be classified as clinically indicated* or not clinically indicated by the investigator prior to angiography. *Clinically indicated revascularization: A revascularization is considered clinically indicated if angiography shows a percent diameter stenosis ≥ 50% and if one of the following occurs: (1) A positive history of recurrent angina pectoris, presumably related to the target vessel; (2) Objective signs of ischemia at rest (ECG changes) or during exercise test (or equivalent), presumably related to the target vessel; (3) Abnormal results of any invasive functional diagnostic test (eg, Doppler flow velocity reserve, fractional flow reserve); (4) A revascularization with a diameter stenosis ≥ 70% even in the absence of the above-mentioned ischemic signs or symptoms.

Stroke

Stroke was defined as a sudden focal neurologic deficit of presumed cerebrovascular etiology that persisted beyond 24 hours and was not due to another identifiable cause. An event matching this definition but lasting less than 24hours was considered to be a transient ischemic attack. Brain imaging (computed tomography o magnetic resonance imaging) was recommended for all suspected strokes.

New onset diabetes mellitus

New-onset diabetes mellitus was defined as initiating antidiabetes medication according to annual medication inventories or fasting plasma glucose > 125mg/dl. Once an individual was defined as having diabetes by either criterion, they were considered to have diabetes throughout follow-up.

Deep vein thrombosis

Deep vein thrombosis was defined as a positive duplex ultrasound or venogram or computed tomography.

Pulmonary thromboembolism

Pulmonary thromboembolism was determined using results of computed tomography, ventilation/perfusion scan, or angiography. thrombosis events were classified as idiopathic or secondary (occurring within 90 days of major trauma, surgery, or marked immobility or associated with active cancer or chemotherapy)

Percutaneous trans-luminal angioplasty on peripheral artery obstructive disease

Percutaneous trans-luminal angioplasty on peripheral artery obstructive disease was defined as recanalization of pelvic and leg arteries in patients with intermittent claudication, rest pain, and /or ischemic ulceration, in addition to stenosis, total occlusions can be recanalized.

Aortic intervention or operation

Surgical or interventional repair of aortic dilatation or dissection.

ESRD

It was not included temporary renal replacement therapy due to acute renal failure associated with other clinical situation.

Aminotransferase elevation:

Definition of Aminotransferase elevation was Aminotransferase increase from baseline and > 3 x ULN (upper limit of normal).

Creatinine kinase elevation:

Definition of Creatine kinase elevation was Creatine kinase increase from baseline and > 5 x ULN (upper limit of normal).

Muscle associated adverse events:

Muscle-associated AEs as myalgia, muscle spam, muscle weakness, musculoskeletal

discomfort, musculoskeletal pain, musculoskeletal stiffness, arthralgia, rhabdomyolysis

Increase of creatinine:

Definition of creatinine increase was creatinine 50% increase from baseline and > ULN (upper limit of normal).

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3. Summary of protocol changes

Amendments	Before the change	After the change	Rationale
Initial submission (31 August 2015)			
Change of study title (22 October 2015)	Comparing the Intensity-based statin therapy with attained low-density lipoprotein cholesterol based statin therapy in patients with coronary artery disease: Statin Strategy Proposal	Low-density lipoprotein cholesterol-targeting statin therapy versus intensity-based statin therapy in patients with coronary artery disease: a randomized comparison trial [Lodestar trial]	In order to clarify the objective of the trial, the title was changed.
Specification of study duration (4 April 2016)	Overall study will require 60 months to complete, including 24 months of recruitment and 36 months of follow-up, followed by close out and reporting of final results.	Patient enrollment: September 19, 2015 ~ March 31, 2021 Follow-up duration: 3 years Total duration of the study: September 19, 2015 ~ March 31, 2024	Rather than describing the study duration in an unclear manner, it has been specified with expected dates and years.
Change in DSMB members (9 June 2016)	Severance Hospital, Seoul: Sang Hak Lee, MD; Geu-Ru Hong, MD; Jae Sun Uhm, MD	Yongin Severance Hospital, Yongin: Jae Sun Uhm, MD Ewha Womans Mokdong Hospital, Seoul: Junbeom Park, MD Chung-Ang University Hospital, Seoul: Iksung Cho, MD Severance hospital, Seoul: Dong-Ho Shin, MD	In order to obtain high quality data, the members were changed to physicians who did not belong to participating centers.
Change in participating centers (16 August 2016) (8 March 2019) (6 January 2020)	1. Yonsei University Severance Hospital 2. Gangnam Severance Hospital 3. Inje University Sanggye Paik Hospital 4. Inje University Ilsan Paik Hospital 5. Myong Ji Hospital 6. Sejong General Hospital 7. Gachon University Gil medical Center 8. Seoul Eulji Hospital 9. Intl. St. Mary`s Hospital 10. Jeju national University Hospital	1. Yonsei University Severance Hospital 2. Gangnam Severance Hospital 3. Inje University Ilsan Paik Hospital 4. Myong Ji Hospital 5. Gachon University Gil medical Center 6. Jeju national University Hospital 7. Kangbuk Samsung Hospital 8. Inje University Busan Paik Hospital 9. Wonju Severance Christian Hospital 10. Chosun University Hospital 11. Keimyung University Dongsan Medical Center 12. Daegu Catholic University Medical Center	Four centers from initial protocol did not participate and six centers additionally participated in the trial. Eventually, the trial was conducted at 12 centers in Korea.

Specification of exclusion criteria (30 November 2016)	4.1.2. Exclusion criteria - Pregnant women or women with potential childbearing. - Patients with severe adverse events or hypersensitive to statin. - Patients receiving drug that have a drug interaction with statin (strong inhibitor of cytochrome p-450 3A4 or 2C9). - Life expectancy <3 years. - Severe hepatic dysfunction (3 times normal reference values).	4.1.2. Exclusion criteria - Pregnant women or women with potential childbearing during the study period. - Patients with severe adverse events or hypersensitive to statin. - Patients receiving drug that have a drug interaction with statin (strong inhibitor of cytochrome p-450 3A4 or 2C9). - Patients with risk factors for myopathy; hereditary muscle disorder, hypothyroidism, alcohol use disorder, severe hepatic dysfunction (3 times normal reference values) or rhabdomyolysis. - Life expectancy <3 years. - Patient with who cannot be followed up for more than 1 year. - Patients who cannot understand the consent form.	In order to exclude the patients who may have potential harm to statins, cannot be followed up sufficiently, or cannot understand the informed consent, exclusion criteria were more properly specified.
Adding additional clinical event in the secondary endpoints (6 June 2017)	Secondary endpoint variables - Newly diagnosed DM after study enrollment - Hospitalization due to heart failure - Deep vein thrombosis or Pulmonary thromboembolism - Percutaneous trans-luminal angioplasty on peripheral artery obstructive disease - Aortic intervention or operation - ESRD - The rate of statin treatment discontinuation - Composite of laboratory abnormality: • Aminotransferase elevation: (ALT > 3 x ULN) • Creatine kinase elevation: (CK>5 x ULN) • Increase of creatinine	Secondary endpoint variables - Newly diagnosed DM after study enrollment - Hospitalization due to heart failure - Deep vein thrombosis or Pulmonary thromboembolism - Percutaneous trans-luminal angioplasty on peripheral artery obstructive disease - Aortic intervention or operation - ESRD - The rate of statin treatment discontinuation - Cataract operation - Composite of laboratory abnormality: • Aminotransferase elevation: (ALT > 3 x ULN) • Creatine kinase elevation: (CK>5 x ULN) • Increase of creatinine	Due to the possible association between the use of statins and risk of cataracts, cataract operation was added in the secondary endpoints as a clinical adverse event (JAMA Ophthalmol. 2013;131:1427-1434).
Description for clinical event adjudication (6 January 2020)	-	7.6. Clinical event adjudication The Clinical Events Adjudication Committee (CEAC) is comprised of interventional and non-interventional cardiologists who are not participants in the study. The CEAC is charged with the development of specific criteria used for	For the purpose of adjudicating the clinical events in objective manner, the clinical events adjudication committee

	the categorization of clinical events and clinical endpoints in the study which are based on protocol. At the onset of the trial, the CEAC will establish explicit rules outlining the minimum amount of date required, and the algorithm followed in order to classify a clinical event. All members of the CEAC will be blinded to the primary results of the trial. The CEAC will meet regularly to review and adjudicate all clinical events. The Committee will also review and rule on all deaths that occur throughout the trial. Severance Cardiovascular Hospital, Seoul — Sang Hak Lee, MD (Chair) Kyung Hee University Hospital — Jung-Myung Lee, MD Kwan Dong University Hospital — Hyoung-Bok Park, MD Ehwa Women's University Seoul Hospital — Choongki Kim, MD	(CEAC) was set up during the initial study design. However, details regarding CEAC and their roles have been accidently not included in the former protocol. Therefore, the corresponding contents were added.
Specification of statistical analyses plan (11 August 2022)	For secondary endpoints, the incidence or cumulative incidences of each endpoint using a Kaplan-Meier plot will be calculated for comparisons. Missing variables will not be imputed for planned analyses, except where otherwise specified. The patient with the missing values will be excluded from the variable-related analysis but included in the analysis not related to the missing variable. For the study endpoints, patients lost to follow-up and subsequently lost to assessment of primary endpoint, will be considered to be censored in the estimation of Kaplan-Meier event rates. Subgroup analysis will be made to compare the HR of experimental arm against control arm stratified by pre-specified subgroups; age (<65 vs. ≥65 years), sex (male vs. female), body mass index (<25 vs. ≥25 kg/m2), diabetes (Yes vs. No), hypertension (Yes vs. No), chronic kidney disease (Yes vs. No), clinical presentation (angina vs. NSTEMI/STEMI), and baseline LDL-C level (<100 vs. ≥100 mg/dL). Demographic and clinical characteristics will be presented to confirm that there is no difference between each administration group by comparing the characteristics of clinical subjects in the treatment group and the control group before enrollment in the clinical trial.	In order to clarify the statistical methods for secondary endpoints analysis, management of missing variables, and subgroup analyses, the corresponding contents were added in the statistical analyses plan.

5. Statistical analysis plan (16 January 2020, First version)

Statistical analysis plan for LODESTAR trial

Statistical analysis plan version 1.0 (16 January 2020)

Low-density lipoprotein cholesterol-targeting statin therapy versus intensity-based statin therapy in patients with coronary artery disease: a randomized comparison trial
[LODESTAR trial]

Trial registration: NCT02579499

This document regarding SAP for LODESTAR trial has been written based on the information included in the study protocol version (6 January 2020).

Contents

1. Introduction

1.1. Study background and rationale

For patients with high-risk of cardiovascular diseases, intensive lowering of low-density lipoprotein cholesterol (LDL-C) levels is recommended, and the use statins has been considered as the cornerstone of lipid-lowering therapy. Particularly, the patients with clinical atherosclerotic cardiovascular disease (ASCVD) including coronary artery disease are considered as very high-risk for adverse cardiovascular events and high-intensity statins are likely to be required under the concept of “the lower, the better” for achieving lower LDL-C levels. However, there have been a controversy whether to focus on achieving LDL-C levels to specific target goals or to focus on simply maintaining high-intensity statins in patients with clinical ASCVD. Meanwhile, in the majority of the randomized trials regarding statin therapy in patients with coronary artery disease, fixed-dose strategies with high-intensity statins were used and demonstrated favorable cardiovascular outcomes compared with lower-intensity statins. However, there are no studies comparing clinical outcomes between fixed-dose high-intensity statin strategy versus targeted LDL-C level strategy.

1.2. Study objectives

The aim of this study is to compare clinical efficacy and safety of targeting LDL-C level <70 mg/dL statin therapy (targeted statin therapy group) versus non-targeting LDL-C level high-intensity statin therapy (non-targeted high-intensity statin therapy group) in patients with coronary artery disease. The primary endpoint is major adverse cardiac and cerebrovascular events, defined as a composite of all-cause death, myocardial infraction (MI), stroke, and any coronary revascularization at 3 years. Secondary endpoints include the occurrence of (1) new-onset diabetes mellitus, (2) hospitalization due to heart failure, (3) deep vein thrombosis or pulmonary thromboembolism, (4) endovascular revascularization of peripheral artery disease, (5) aortic intervention or surgery, (6) end-stage renal disease, (7) discontinuation of study drugs due to intolerance, (8) cataract operation, and (9) composite of laboratory abnormality.

1.3. Study hypothesis

The primary hypothesis of LODESTAR trial is that the targeted statin therapy strategy would be non-inferior to the non-targeted high-intensity statin therapy strategy in the

patients with coronary artery disease in terms of long-term clinical outcomes as an intention-to-treat population. Non-inferiority of targeted statin therapy compared to non-targeted high-intensity statin therapy regarding primary endpoint will be evaluated to prove the primary hypothesis of this study.

2. Trial methods

2.1. Study design and randomization

LODESTAR trial is an investigator-initiated, multicenter, randomized, open-label clinical trial conducting at 12 centers in Korea which is designed to answer to the following question: is LDL-C targeted statin therapy non-inferior to non-targeted high-intensity statin therapy in terms of 3-year composite cardiovascular events in patients with coronary artery disease.

All eligible patients with clinically diagnosed coronary artery disease including stable coronary artery disease and acute coronary syndrome (unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction) was screened and enrolled according to inclusion/exclusion criteria after voluntary agreement with informed consent. The eligible patients were randomized in a 1:1 manner to receive either targeted statin therapy (LDL-C goal of <70 mg/dL) or non-targeted high-intensity statin therapy (rosuvastatin 20 mg or atorvastatin 40mg once daily). A web-response permuted-block randomization (mixed blocks of 4 or 6) was used at each participating site to allocate the patients, stratified by LDL-C levels ≥100 mg/dL, acute coronary syndrome, and presence of diabetes mellitus at baseline. In addition, in each therapy group, the patients were also randomized in a 1:1 manner to receive two different types of statins (rosuvastatin or atorvastatin). The allocation sequence was computer generated by an external programmer not involved in the trial, and physicians or research coordinators accessed the web-response system.

2.2. Sample size

The expected event rate of primary endpoint per year was 4% in the non-targeted high-intensity statin therapy group, based on the previous trials regarding the statin-based intensive lipid-lowering therapy in patients with coronary artery disease. It was assumed that the two therapies had equivalent efficacy, therefore, the expected event rate of primary endpoint at 3 years of follow-up was estimated as 12% in each therapy

group, respectively. A non-inferiority margin of 3.0% points was primarily selected with a consideration that this is clinically no differences between two groups. Based on the non-inferiority hypothesis of 3.0% margin, a total of 4336 patients were required considering a 2.5% one-sided alpha error rate, 80% power, and 15% follow-up loss. Considering the balance of two different types of statins (rosuvastatin or atorvastatin), final study population consisted of 4400 patients. Further details regarding the sample size calculation is provided in the clinical trial protocol.

2.3. Interim analyses and guidelines for stopping the study

There was no planned formal interim analysis and guidelines for stopping the study. However, the data and safety monitoring board (DSMB) reviewed the safety data in a blind manner and the DSMB statistician provided unblinded summary tables. The DSMB discussed and determined whether the stopping in advance is required or there is a safety concern. Until 21 August 2022, there was no advance stopping of the study.

2.4. Timing for assessment of outcomes and lipid profiles

Patients have been scheduled for follow-up visits at 6 weeks; 3, 6, 12, 24 and 36 months, to assess general health status, use of drugs, and the occurrence of clinical endpoints or adverse events. Serial follow-up of patients' lipid profiles has been performed at 6 weeks; 12, 24, and 36 months, to confirm the attained LDL-C levels.

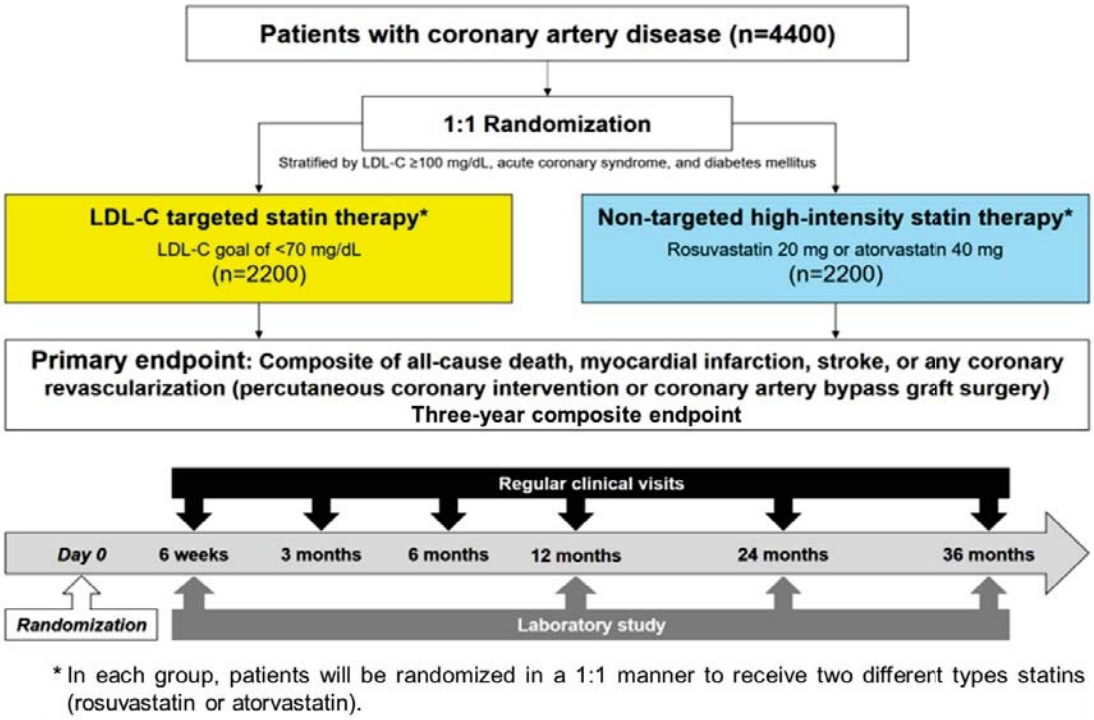
2.5. Timing for analysis

The first patient of LODESTAR trial was enrolled in September 2016 and the last patient was enrolled in November 2019. Completion of 3-year clinical follow-up is expected by October 2022. Final analysis is planned to be performed in November 2022 after the database is locked and cleaned.

Table. Patients Schedule for clinical and laboratory follow-up

	Follow-up					
	6W ± 2 W	3 M ± 1 M	6 M ± 1 M	12 M ± 2 M	24 M ± 2 M	36 M ± 2 M
Vital status & physical exam	O	O	O	O	O	O
Current medications	O	O	O	O	O	O
Clinical endpoints	O	O	O	O	O	O
Serious adverse events	O	O	O	O	O	O
CBC, routine chemistry, lipid profile, creatine kinase (CK), hs-CRP	O (Lipid profile, AST/ALT, CK only)	O (Lipid profile, AST/ALT, CK only, and optional)	O (Lipid profile, AST/ALT, CK only, and optional)	O	O	O
HbA1C				O	O	O

Figure. LODESTAR trial study design and flow diagram



* In each group, patients will be randomized in a 1:1 manner to receive two different types statins (rosuvastatin or atorvastatin).

3. Statistical principles

3.1. General principles

Statistical analysis for LODESTAR trial will be performed by independent statisticians. Categorical data on demographic, medication, and procedural characteristics will be presented as numbers (percentages), and compared using the chi-square or Fisher's exact test. Continuous data will be presented as mean ± standard deviation or median (interquartile range) for normal or skewed distributions, and compared using the Student's t-test or Mann-Whitney U test. The cumulative incidence of the primary endpoint will be estimated at 3 years, and Kaplan–Meier curves for time-to-event analysis will be plotted based on the time of enrollment to the occurrence of the first event of interest during follow-up. P-value <0.05 will be considered statistically significant and there will be no adjustment for multiple comparisons.

3.2. Test for non-inferiority

A test of non-inferiority will be performed for the primary endpoint and it was predetermined that non-inferiority would be declared if the upper normal limit of the one-sided 97.5% CI for the difference in incidence of primary endpoint between the two therapy groups was <3.0%.

3.3. Study population for analysis

The primary analysis will be performed in the intention-to-treat population with all patients randomly assigned to a therapy group.

The analysis will be also performed in the per-protocol population after excluding the patients who were not given the allocated therapy; (i) a total period of the discontinued the statin therapy >5% of a total follow-up period in both groups (not due to adverse events), (ii) non-up-titration despite of non-achievement of a target goal in the targeted statin group, and (iii) non-maintenance of high-intensity statin in the non-targeted high-intensity statin group.

4. Trial population

4.1. Eligibility for the trial

Patients with clinically diagnosed coronary artery disease including stable coronary

artery disease and acute coronary syndrome that requires intensive lowering of LDL-C levels according to the American and European dyslipidemia guidelines were eligible to participate in LODESTAR trial. Full details regarding the inclusion and exclusion criteria for the trial is provided in the clinical trial protocol. The trial was approved by the institutional review board of each participating center and followed the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before participation in the trial

4.2. Follow-up after enrollment

After enrollment in the trial, the reasons for not receiving the allocated therapy and reasons for not continuing the allocated therapy during follow-up (i.e. death, follow-up loss, withdrawal of consent) will be investigated and provided by each therapy group according to consort flow diagram.

4.3. Baseline characteristics

Baseline characteristics of patients will be presented based on the allocated therapy groups, primarily in the intention-to-treat population. Categorical variables will be presented as numbers (percentages) and continuous variables will be presented as mean ± standard deviation or median (interquartile range) depending on their distribution. The number of missing data will be reported. No formal statistical comparisons will be performed. Details regarding baseline characteristics are provided in Table.

Table. Baseline characteristics of the intention-to-treat population

Characteristic	Targeted statin therapy	Non-targeted high-intensity statin therapy
Age		
Sex		
Weight		
Height		
Body-mass index		
Hypertension		
Diabetes		
Diabetes with insulin treatment		

Chronic kidney disease
End-stage kidney disease on dialysis
Estimated glomerular filtration rates
Current smoker
Previous stroke
Previous PCI
Previous CABG
Clinical presentation at randomization
    Acute myocardial infarction within 1 year
    Unstable angina or revascularization within 1 year
    >1 year after myocardial infarction
    >1 year after unstable angina or revascularization
    Detection of CAD at screening without symptoms
Lipid lowering therapy before randomization
    Statin
        None
        Low-intensity statin
        Moderate-intensity statin
        High-intensity statin
    Ezetimibe
Lipid levels
    Low-density lipoprotein cholesterol
    High-density lipoprotein cholesterol
    Total cholesterol
    Triglycerides

5. Data analysis

5.1. Study outcomes

The Clinical Events Adjudication Committee (CEAC) is comprised of interventional and non-interventional cardiologists who are not participants in the trial and blinded to therapy allocation. The CEAC is charged with the development of specific criteria used for the categorizing clinical events in the study which are based on the study protocol. At the onset of the trial, the CEAC will establish explicit rules outlining the minimum amount of date required, and the algorithm followed in order to classify clinical events. All members of the CEAC will be blinded to the primary results of the trial. The CEAC will hold a meeting regularly to review and adjudicate all clinical events. The Committee will also review and oversee all deaths that occur throughout the trial (cardiovascular death vs. non-cardiovascular death).

5.1.1. Primary endpoint

Primary endpoint (major adverse cardiac and cerebrovascular events) is defined as time to first occurrence of all-cause death, MI, stroke, or any coronary revascularization during 3 years of follow-up.

5.1.2. Secondary endpoints

Secondary endpoints are defined as time to first occurrence of following events during 3 years of follow-up.

(1) New-onset diabetes mellitus
(2) Hospitalization due to heart failure
(3) Deep vein thrombosis or pulmonary thromboembolism
(4) Endovascular revascularization of peripheral artery disease
(5) Aortic intervention or surgery
(6) End-stage renal disease
(7) Discontinuation of study drugs due to intolerance
(8) Cataract operation
(9) Composite of laboratory abnormality

Details regarding the definition of individual clinical endpoints are provided in the appendix.

5.2. Methods for analysis

The cumulative incidence of the primary endpoint will be estimated at 3 years, and Kaplan–Meier curves for time-to-event analysis will be plotted based on the time of enrollment to the occurrence of the first event of interest during follow-up. Event rates between the two therapy groups will be compared using log-rank tests, and HRs with 95% CIs will be estimated using the Cox regression analysis. A test of non-inferiority will be performed for the primary endpoint and it is predetermined that non-inferiority would be declared if the upper normal limit of the one-sided 97.5% CI for the difference in incidence of primary endpoint between the two groups was <3.0%.

The primary analysis will be performed in the intention-to-treat population with all patients randomly assigned to a therapy group. The analysis will be also performed

in the per-protocol population after excluding the patients who were not given the allocated therapy; (i) a total period of the discontinued the statin therapy >5% of a total follow-up period in both groups (not due to adverse events), (ii) non-up-titration despite of non-achievement of a target goal in the targeted statin group, and (iii) non-maintenance of high-intensity statin in the non-targeted high-intensity statin group.

5.3. Additional analysis

The use of lipid-lowering medications (statins, ezetimibe, and others) and other cardiovascular medications (antiplatelet agents, antihypertensive agents, and others) will be reported for each therapy group without formal statistical comparison.

The levels of LDL-C during follow-up (6 weeks, 12, 24, and 36 months) will be compared using the Student's t-test and proportion patients with LDL-C levels <70 mg/dL will be compared using the chi-square test. The levels of other lipid profiles (total cholesterol, high-density lipoprotein cholesterol, triglyceride) will be compared using the Student's t-test.

5.4. Statistical software

SAS software (version 9.2, SAS Institute, Cary, NC, USA) will be primarily used for data analysis. R 3.5.3 software (R foundations for Statistical Computing, Vienna, Austria) with specific packages will be used in needed.

6. References

1. Crowe BJ, Xia HA, Berlin JA, Watson DJ, Shi H, Lin SL, Kuebler J, Schriver RC, Santanello NC, Rochester G, Porter JB, Oster M, Mehrotra DV, Li Z, King EC, Harpur ES, Hall DB. Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. Clin Trials 2009;6(5):430-440.
2. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA 2012;308(24):2594-604.

7. Appendix - Outcomes definitions for LODESTAR trial

7.1. Classification of death

Death is classified as cardiovascular death and non-cardiovascular death. Cardiovascular death is defined as death due to myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, and any case of death in which a cardiovascular cause cannot be excluded as adjudicated by a CEAC.

7.2. Myocardial infarction

Myocardial infarction is defined based on clinical symptoms, electrocardiogram changes, or abnormal findings on imaging studies, combined with an increase in the creatine kinase myocardial band fraction above the upper normal limit or an increase in troponin-T or I level > 99th percentile of the upper normal limit.

7.3. Stroke

Stroke is defined as an acute cerebrovascular event resulting in a neurologic deficit >24 hours or the presence of acute infarction demonstrated by imaging studies.

7.4. Any coronary revascularization

Any coronary revascularization includes percutaneous coronary intervention and coronary artery bypass graft surgery.

7.5. New-onset diabetes mellitus

New-onset diabetes mellitus is defined as new initiation of antidiabetic drugs or fasting plasma glucose level ≥126 mg/dL. A post-hoc analysis will be performed to also include patients identified to have a HbA1c level ≥6.5% during the study period as having new-onset diabetes mellitus, based on the review of the trial database.

7.6. Hospitalization due to heart failure

Hospitalization due to heart failure is defined as a hospitalization which requires at least an overnight stay in hospital owing to substantial worsening of heart failure symptoms and/or signs which requires the augmentation of oral medications or new administration of intravenous heart failure treatment such as diuretics, inotropes, or

vasodilators.

7.7. Deep vein thrombosis

Deep vein thrombosis is defined as formation of thrombus in the lower extremity deep veins, demonstrated by imaging studies such as compression ultrasonography, contrast venography, or computed tomography.

7.8. Pulmonary thromboembolism

Pulmonary thromboembolism is defined as formation of thrombus in pulmonary arteries demonstrated by imaging studies such as ventilation-perfusion lung scan, pulmonary angiography, or computed tomography.

7.9. Aortic intervention or surgery

Aortic intervention or surgery includes any endovascular procedure or surgery for treating disease aorta.

7.10. End-stage renal disease

End stage renal disease is defined as stage 5 according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of the chronic kidney disease (estimated glomerular filtration rate <15 mL/min/1.73m2 of body surface area or requirement for dialysis irrespective of glomerular filtration rate).

7.11. Aminotransferase elevation

Aminotransferase increase from baseline and > 3 x ULN (upper limit of normal).

7.12. Creatinine kinase elevation

Creatine kinase increase from baseline and > 5 x ULN (upper limit of normal).

7.13. Increase of creatinine:

Definition of creatinine increase was creatinine 50% increase from baseline and > ULN (upper limit of normal).

6. Statistical analysis plan (13 August 2022, Last version)

Statistical analysis plan for LODESTAR trial

Statistical analysis plan_version 1.1 (13 August 2022)

Low-density lipoprotein cholesterol-targeting statin therapy versus intensity-based statin therapy in patients with coronary artery disease: a randomized comparison trial
[LODESTAR trial]

Trial registration: NCT02579499

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Contents

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The aim of this study is to compare clinical efficacy and safety of targeting LDL-C level <70 mg/dL statin therapy (targeted statin therapy group) versus non-targeting LDL-C level high-intensity statin therapy (non-targeted high-intensity statin therapy group) in patients with coronary artery disease. The primary endpoint is major adverse cardiac and cerebrovascular events, defined as a composite of all-cause death, myocardial infraction (MI), stroke, and any coronary revascularization at 3 years. Secondary endpoints include the occurrence of (1) new-onset diabetes mellitus, (2) hospitalization due to heart failure, (3) deep vein thrombosis or pulmonary thromboembolism, (4) endovascular revascularization of peripheral artery disease, (5) aortic intervention or surgery, (6) end-stage renal disease, (7) discontinuation of study drugs due to intolerance, (8) cataract operation, and (9) composite of laboratory abnormality.

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2.2. Sample size

The expected event rate of primary endpoint per year was 4% in the non-targeted high-intensity statin therapy group, based on the previous trials regarding the statin-based intensive lipid-lowering therapy in patients with coronary artery disease. It was assumed that the two therapies had equivalent efficacy, therefore, the expected event rate of primary endpoint at 3 years of follow-up was estimated as 12% in each therapy

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2.4. Timing for assessment of outcomes and lipid profiles

Patients have been scheduled for follow-up visits at 6 weeks; 3, 6, 12, 24 and 36 months, to assess general health status, use of drugs, and the occurrence of clinical endpoints or adverse events. Serial follow-up of patients' lipid profiles has been performed at 6 weeks; 12, 24, and 36 months, to confirm the attained LDL-C levels.

2.5. Timing for analysis

The first patient of LODESTAR trial was enrolled in September 2016 and the last patient was enrolled in November 2019. Completion of 3-year clinical follow-up is expected by October 2022. Final analysis is planned to be performed in November 2022 after the database is locked and cleaned.

Table. Patients Schedule for clinical and laboratory follow-up

	Follow-up					
	6W ± 2 W	3 M ± 1 M	6 M ± 1 M	12 M ± 2 M	24 M ± 2 M	36 M ± 2 M
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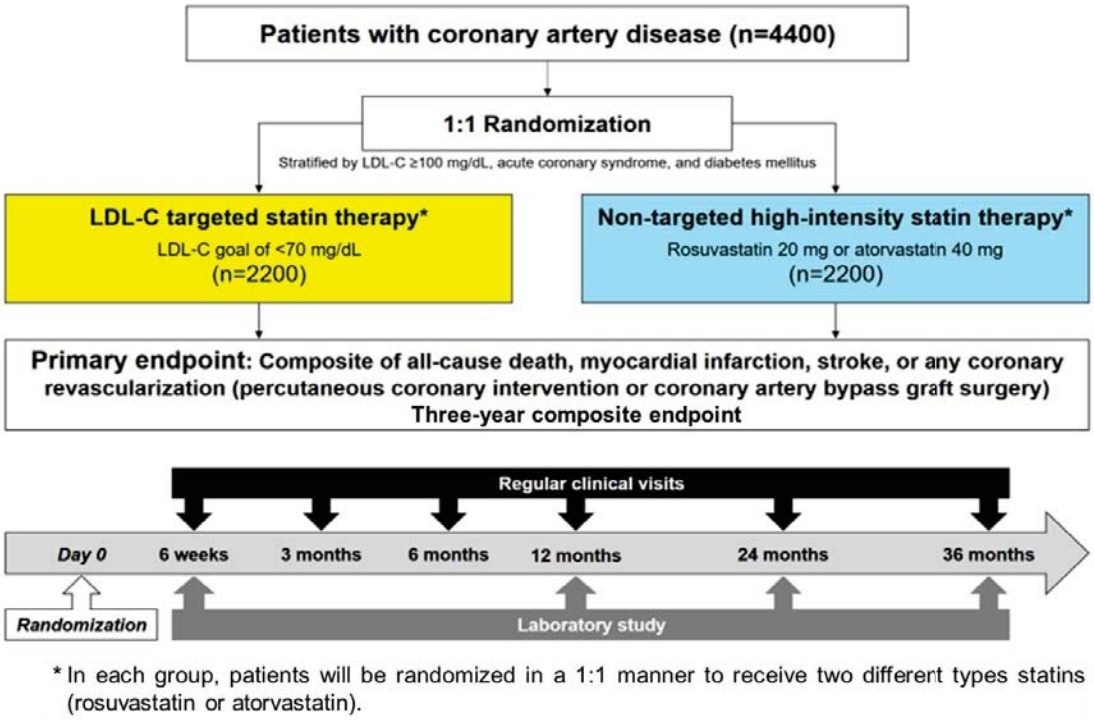
Current medications	O	O	O	O	O	O
Clinical endpoints	O	O	O	O	O	O
Serious adverse events	O	O	O	O	O	O
CBC, routine chemistry, lipid profile, creatine kinase (CK), hs-CRP	O (Lipid profile, AST/ALT, CK only)	O (Lipid profile, AST/ALT, CK only, and optional)	O (Lipid profile, AST/ALT, CK only, and optional)	O	O	O
HbA1C				O	O	O

Figure. LODESTAR trial study design and flow diagram



* In each group, patients will be randomized in a 1:1 manner to receive two different types statins (rosuvastatin or atorvastatin).

3. Statistical principles

3.1. General principles

Statistical analysis for LODESTAR trial will be performed by independent statisticians. Categorical data on demographic, medication, and procedural characteristics will be presented as numbers (percentages), and compared using the chi-square or Fisher's exact test. Continuous data will be presented as mean ± standard deviation or median (interquartile range) for normal or skewed distributions, and compared using the Student's t-test or Mann-Whitney U test. The cumulative incidence of the primary endpoint will be estimated at 3 years, and Kaplan–Meier curves for time-to-event analysis will be plotted based on the time of enrollment to the occurrence of the first event of interest during follow-up. P-value <0.05 will be considered statistically significant and there will be no adjustment for multiple comparisons.

3.2. Test for non-inferiority

A test of non-inferiority will be performed for the primary endpoint and it was predetermined that non-inferiority would be declared if the upper normal limit of the one-sided 97.5% CI for the difference in incidence of primary endpoint between the two therapy groups was <3.0%.

3.3. Study population for analysis

The primary analysis will be performed in the intention-to-treat population with all patients randomly assigned to a therapy group.

The analysis will be also performed in the per-protocol population after excluding the patients who were not given the allocated therapy; (i) a total period of the discontinued the statin therapy >5% of a total follow-up period in both groups (not due to adverse events), (ii) non-up-titration despite of non-achievement of a target goal in the targeted statin group, and (iii) non-maintenance of high-intensity statin in the non-targeted high-intensity statin group.

4. Trial population

4.1. Eligibility for the trial

Patients with clinically diagnosed coronary artery disease including stable coronary

artery disease and acute coronary syndrome that requires intensive lowering of LDL-C levels according to the American and European dyslipidemia guidelines were eligible to participate in LODESTAR trial. Full details regarding the inclusion and exclusion criteria for the trial is provided in the clinical trial protocol. The trial was approved by the institutional review board of each participating center and followed the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients before participation in the trial

4.2. Follow-up after enrollment

After enrollment in the trial, the reasons for not receiving the allocated therapy and reasons for not continuing the allocated therapy during follow-up (i.e. death, follow-up loss, withdrawal of consent) will be investigated and provided by each therapy group according to consort flow diagram.

4.3. Baseline characteristics

Baseline characteristics of patients will be presented based on the allocated therapy groups, primarily in the intention-to-treat population. Categorical variables will be presented as numbers (percentages) and continuous variables will be presented as mean ± standard deviation or median (interquartile range) depending on their distribution. The number of missing data will be reported. No formal statistical comparisons will be performed. Details regarding baseline characteristics are provided in Table.

Table. Baseline characteristics of the intention-to-treat population

Characteristic	Targeted statin therapy	Non-targeted high-intensity statin therapy
Age		
Sex		
Weight		
Height		
Body-mass index		
Hypertension		
Diabetes		

Diabetes with insulin treatment
Chronic kidney disease
End-stage kidney disease on dialysis
Estimated glomerular filtration rates
Current smoker
Previous stroke
Previous PCI
Previous CABG
Clinical presentation at randomization
    Acute myocardial infarction within 1 year
    Unstable angina or revascularization within 1 year
    >1 year after myocardial infarction
    >1 year after unstable angina or revascularization
    Detection of CAD at screening without symptoms
Lipid lowering therapy before randomization
    Statin
        None
        Low-intensity statin
        Moderate-intensity statin
        High-intensity statin
    Ezetimibe
Lipid levels
    Low-density lipoprotein cholesterol
    High-density lipoprotein cholesterol
    Total cholesterol
    Triglycerides

5. Data analysis

5.1. Study outcomes

The Clinical Events Adjudication Committee (CEAC) is comprised of interventional and non-interventional cardiologists who are not participants in the trial and blinded to therapy allocation. The CEAC is charged with the development of specific criteria used for the categorizing clinical events in the study which are based on the study protocol. At the onset of the trial, the CEAC will establish explicit rules outlining the minimum amount of date required, and the algorithm followed in order to classify clinical events. All members of the CEAC will be blinded to the primary results of the trial. The CEAC will hold a meeting regularly to review and adjudicate all clinical events. The Committee will also review and oversee all deaths that occur throughout the trial (cardiovascular death vs. non-cardiovascular death).

5.1.1. Primary endpoint

Primary endpoint (major adverse cardiac and cerebrovascular events) is defined as time to first occurrence of all-cause death, MI, stroke, or any coronary revascularization during 3 years of follow-up.

5.1.2. Secondary endpoints

Secondary endpoints are defined as time to first occurrence of following events during 3 years of follow-up.

(1) New-onset diabetes mellitus
(2) Hospitalization due to heart failure
(3) Deep vein thrombosis or pulmonary thromboembolism
(4) Endovascular revascularization of peripheral artery disease
(5) Aortic intervention or surgery
(6) End-stage renal disease
(7) Discontinuation of study drugs due to intolerance
(8) Cataract operation
(9) Composite of laboratory abnormality

Details regarding the definition of individual clinical endpoints are provided in the appendix.

5.2. Methods for analysis

The cumulative incidence of the primary endpoint will be estimated at 3 years, and Kaplan–Meier curves for time-to-event analysis will be plotted based on the time of enrollment to the occurrence of the first event of interest during follow-up. Event rates between the two therapy groups will be compared using log-rank tests, and HRs with 95% CIs will be estimated using the Cox regression analysis. A test of non-inferiority will be performed for the primary endpoint and it is predetermined that non-inferiority would be declared if the upper normal limit of the one-sided 97.5% CI for the difference in incidence of primary endpoint between the two groups was <3.0%.

The primary analysis will be performed in the intention-to-treat population with all patients randomly assigned to a therapy group. The analysis will be also performed

in the per-protocol population after excluding the patients who were not given the allocated therapy; (i) a total period of the discontinued the statin therapy >5% of a total follow-up period in both groups (not due to adverse events), (ii) non-up-titration despite of non-achievement of a target goal in the targeted statin group, and (iii) non-maintenance of high-intensity statin in the non-targeted high-intensity statin group.

5.3. Subgroup analysis

The following pre-specified subgroups will be explored:

(1) Age (<65 vs. ≥65 years)

(2) Sex (male vs. female)

(3) Body mass index (<25 vs. ≥25 kg/m^2)

(4) Diabetes (Yes vs. No)

(5) Hypertension (Yes vs. No)

(6) Chronic kidney disease (Yes vs. No)

(7) Clinical presentation (angina vs. non-ST-elevation myocardial infarction /ST-elevation myocardial infarction)

(8) Baseline LDL-C level (<100 vs. ≥100 mg/dL)

The consistency of therapy effect will be evaluated regarding the primary endpoint. Therapy effect size (HR) will be investigated in each subgroup and corresponding forest-plot will be plotted. For each subgroup, P-values for interaction between therapy and subgroup will be calculated using Cox proportional hazard model.

5.4. Missing data management

Full attempts will be carried out to capture missing data for the trial prior to database lock. Missing variables will not be imputed for planned analyses. The patient with the missing values will be excluded from the variable-related analysis but included in the analysis not related to the missing variable. For the study endpoints, patients with missing primary and secondary endpoint data were censored at the time of withdrawal of consent or loss to follow-up.

5.5. Additional analysis

The use of lipid-lowering medications (statins, ezetimibe, and others) and other

cardiovascular medications (antiplatelet agents, antihypertensive agents, and others) will be reported for each therapy group without formal statistical comparison.

The levels of LDL-C during follow-up (6 weeks, 12, 24, and 36 months) will be compared using the Student's t-test and proportion patients with LDL-C levels <70 mg/dL will be compared using the chi-square test. The levels of other lipid profiles (total cholesterol, high-density lipoprotein cholesterol, triglyceride) will be compared using the Student's t-test.

5.6. Statistical software

SAS software (version 9.2, SAS Institute, Cary, NC, USA) will be primarily used for data analysis. R 3.5.3 software (R foundations for Statistical Computing, Vienna, Austria) with specific packages will be used in needed.

6. References

1. Crowe BJ, Xia HA, Berlin JA, Watson DJ, Shi H, Lin SL, Kuebler J, Schriver RC, Santanello NC, Rochester G, Porter JB, Oster M, Mehrotra DV, Li Z, King EC, Harpur ES, Hall DB. Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. Clin Trials 2009;6(5):430-440.
2. Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG; CONSORT Group. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. JAMA 2012;308(24):2594-604.

7. Appendix - Outcomes definitions for LODESTAR trial

7.1. Classification of death

Death is classified as cardiovascular death and non-cardiovascular death. Cardiovascular death is defined as death due to myocardial infarction, sudden cardiac death, heart failure, stroke, cardiovascular procedures, cardiovascular hemorrhage, and any case of death in which a cardiovascular cause cannot be excluded as adjudicated by a CEAC.

7.2. Myocardial infarction

Myocardial infarction is defined based on clinical symptoms, electrocardiogram changes, or abnormal findings on imaging studies, combined with an increase in the creatine kinase myocardial band fraction above the upper normal limit or an increase in troponin-T or I level > 99th percentile of the upper normal limit.

7.3. Stroke

Stroke is defined as an acute cerebrovascular event resulting in a neurologic deficit >24 hours or the presence of acute infarction demonstrated by imaging studies.

7.4. Any coronary revascularization

Any coronary revascularization includes percutaneous coronary intervention and coronary artery bypass graft surgery.

7.5. New-onset diabetes mellitus

New-onset diabetes mellitus is defined as new initiation of antidiabetic drugs or fasting plasma glucose level ≥126 mg/dL. A post-hoc analysis will be performed to also include patients identified to have a HbA1c level ≥6.5% during the study period as having new-onset diabetes mellitus, based on the review of the trial database.

7.6. Hospitalization due to heart failure

Hospitalization due to heart failure is defined as a hospitalization which requires at least an overnight stay in hospital owing to substantial worsening of heart failure symptoms and/or signs which requires the augmentation of oral medications or new administration of intravenous heart failure treatment such as diuretics, inotropes, or

vasodilators.

7.7. Deep vein thrombosis

Deep vein thrombosis is defined as formation of thrombus in the lower extremity deep veins, demonstrated by imaging studies such as compression ultrasonography, contrast venography, or computed tomography.

7.8. Pulmonary thromboembolism

Pulmonary thromboembolism is defined as formation of thrombus in pulmonary arteries demonstrated by imaging studies such as ventilation-perfusion lung scan, pulmonary angiography, or computed tomography.

7.9. Aortic intervention or surgery

Aortic intervention or surgery includes any endovascular procedure or surgery for treating disease aorta.

7.10. End-stage renal disease

End stage renal disease is defined as stage 5 according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of the chronic kidney disease (estimated glomerular filtration rate <15 mL/min/1.73m2 of body surface area or requirement for dialysis irrespective of glomerular filtration rate).

7.11. Aminotransferase elevation

Aminotransferase increase from baseline and > 3 x ULN (upper limit of normal).

7.12. Creatinine kinase elevation

Creatine kinase increase from baseline and > 5 x ULN (upper limit of normal).

7.13. Increase of creatinine:

Definition of creatinine increase was creatinine 50% increase from baseline and > ULN (upper limit of normal).

6. Summary of statistical analysis plan changes

Amendments	Before the change	After the change	Rationale
Initial SAP (16 January 2020)	—	—	—
Specification of data analysis plan (13 August 2022)	—	For secondary endpoints, the incidence or cumulative incidences of each endpoint using a Kaplan-Meier plot will be calculated for comparisons. Missing variables will not be imputed for planned analyses, except where otherwise specified. The patient with the missing values will be excluded from the variable-related analysis but included in the analysis not related to the missing variable. For the study endpoints, patients lost to follow-up and subsequently lost to assessment of primary endpoint, will be considered to be censored in the estimation of Kaplan-Meier event rates. Subgroup analysis will be made to compare the HR of experimental arm against control arm stratified by pre-specified subgroups; age (<65 vs. ≥65 years), sex (male vs. female), body mass index (<25 vs. ≥25 kg/m2), diabetes (Yes vs. No), hypertension (Yes vs. No), chronic kidney disease (Yes vs. No), clinical presentation (angina vs. NSTEMI/STEMI), and baseline LDL-C level (<100 vs. ≥100 mg/dL). Demographic and clinical characteristics will be presented to confirm that there is no difference between each administration group by comparing the characteristics of clinical subjects in the treatment group and the control group before enrollment in the clinical trial.	In order to clarify the statistical methods for secondary endpoints analysis, management of missing variables, and subgroup analyses, the corresponding contents were added.