CLINICAL STUDY

Rationale and Design of Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) Trial

Katsumi Miyauchi,[1] MD, Takeshi Kimura,[2] MD, Hiroaki Shimokawa,[3] MD, Hiroyuki Daida,[1] MD, Satoshi Iimuro,[4] MD, Hiroshi Iwata,[1] MD, Yukio Ozaki,[5] MD, Ichiro Sakuma,[6] MD, Yoshihisa Nakagawa,[7] MD, Kiyoshi Hibi,[8] MD, Takafumi Hiro,[9] MD, Yoshihiro Fukumoto,[10] MD, Seiji Hokimoto,[11] MD, Yasuo Ohashi,[12] PhD, Hiroshi Ohtsu,[13] MSc, Yasushi Saito,[14] MD, Masunori Matsuzaki,[15] MD and Ryozo Nagai,[16] MD
for the REAL-CAD Trial Investigaters

Summary

Large-scale clinical trials in patients in Western countries with coronary artery disease (CAD) have found that aggressive lipid-lowering therapy using high-dose statins reduces cardiovascular (CV) events further than low-dose statins. However, such evidence has not yet been fully established in Asian populations, including in Japan. The Randomized Evaluation of Aggressive or Moderate Lipid-Lowering Therapy with Pitavastatin in Coronary Artery Disease (REAL-CAD) study addresses whether intensification of statin therapy improves clinical outcomes in Japanese patients with CAD.

REAL-CAD is a prospective, multicenter, randomized, open-label, blinded-endpoint, physician-initiated phase 4 trial in Japan. The study will recruit up to 12,600 patients with stable CAD. Patients are assigned to receive either pitavastatin 1 mg/day or pitavastatin 4 mg/day. LDL-C levels are expected to reach approximate mean values of 100 mg/dL in the low-dose pitavastatin group and 80 mg/dL in the high-dose group. The primary endpoint is the time to occurrence of a major CV event, including CV death, non-fatal myocardial infarction, non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization during an average of 5 years. The large number of patients and the long follow-up period in the REAL-CAD study should ensure that there is adequate power to definitively determine if reducing LDL-C levels to approximately 80 mg/dL by high-dose statin can provide additional clinical benefit.

After the study is completed, we will have categorical evidence on the optimal statin dose and target LDL-C level for secondary prevention in Japanese patients.

(Int Heart J 2018; 59: 315-320)

Key words: LDL cholesterol, High-dose statin therapy, Long-term outcomes, Cardiovascular events, Secondary prevention, Myocardial infarction, Unstable angina, Stroke

Cardiovascular (CV) death is an important medical and social problem in Japan and is increasing every year. Although widespread use of new and effective drug treatments and percutaneous coronary intervention (PCI) have improved outcomes in patients with coronary artery disease (CAD), the recurrence rate in patients for secondary prevention remained high compared with patients for primary prevention.[1-3)]

Many epidemiological studies have proven that coronary deaths and CV events are associated with elevated levels of low-density lipoprotein cholesterol (LDL-C). Furthermore, large-scale clinical trials have found that

From the [1]Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine, Tokyo, [2]Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoko, [3]Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine, Miyagi, [4]Teikyo Academic Research Center, Teikyo University, Tokyo, [5]Department of Cardiology, Fujita Health University Hospital, Fujita Health University School of Medicine, Aichi, [6]Caress Sapporo Hokko Memorial Clinic, Hokkaido, [7]Department of Cardiology, Tenri Hospital, Nara, [8]Division of Cardiology, Yokohama City University Medical Center, Kanagawa, [9]Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, [10]Division of Cardiovascular Medicine, Department of Internal Medicine, Kurume University School of Medicine, Fukuoka, [11]Department of Cardiovascular Medicine, Kumamoto University Hospital, Kumamoto, [12]Department of Integrated Science and Technology for Sustainable Society, Chuo University, Tokyo, [13]National Center for Global Health and Medicine, Center for Clinical Sciences, Tokyo, [14]Chiba University, Chiba, [15]St. Hill Hospital, Yamaguchi and [16]Jichi Medical University, Tochigi, Japan.

This study is supported by the Comprehensive Support Project for Clinical Research of Lifestyle-Related Disease of the Public Health Research Foundation (PHRF). The company manufacturing the study drug (Kowa Pharmaceutical Co., Ltd.) was one of the entities providing financial support for the project of PHRF.

Address for correspondence: Katsumi Miyauchi, MD, Department of Cardiovascular Medicine, Juntendo University, 2-1-1, Hongo, Bunkyo-ku, Tokyo, 113-8421, Japan. E-mail: ktmmy@juntendo.ac.jp

Received for publication September 28, 2017. Revised and accepted December 1, 2017.
Released in advance online on J-STAGE March 5, 2018.
doi: 10.1536/ihj.17-557

lipid-lowering therapy using statins reduces CV events.[4-11] In the J-LIT and MUSASHI-AMI studies in Japan, the recurrence risk for CV events was significantly decreased when LDL-C levels were reduced to below 100 mg/dL (2.6 mmol/L) with stain treatment.[1,12] Based on these findings, the guidelines of the Japan Atherosclerosis Society state that LDL-C levels should be 100 mg/dL or lower for secondary prevention.[13] This target is higher than the targets specified in European and former American guidelines.[14,15]

Secondary prevention trials such as the A to Z, TNT, IDEAL, and PROVE-IT studies have compared the rate of CV events between high intensity and moderate intensity lipid-lowering treatments.[16-19] In a meta-analysis of these trials, high intensity lipid-lowering treatment significantly reduced the rate of CV events (by 16%) compared with moderate intensity lipid-lowering therapy.[20] CV events were correlated with LDL-C reduction, both in patients with acute coronary syndrome (ACS) and patients with chronic phase CAD.[21] Therefore, for secondary prevention, European guidelines recommend a target LDL-C of less than 70 mg/dL, and American College of Cardiology (ACC)/American Heart Association (AHA) guideline recommends high-intensity statin therapy.[14,22]

Since the CV event rate in Asian populations is much lower than that in European and American populations,[23,24] it is important to confirm the benefits of statin therapy in Asian populations. In Japan, no large-scale outcome studies on the use of statins for secondary prevention have been conducted up to now. However, several trials have used intravascular ultrasound to show that intensive LDL-C reduction with statins leads to plaque regression. The ESTABLISH, JAPAN-ACS, and COSMOS trials demonstrated that lowering LDL-C to 70-80 mg/dL by aggressive lipid-lowering treatment with moderately high-dose statins significantly reduced coronary plaque volume.[25-27] Moreover, the extended ESTABLISH trial suggested that plaque regression during the randomized period correlated with reduced long-term CV events.[28] Thus, we hypothesize that aggressive lipid-lowering treatment with high-dose statins could improve clinical outcomes in Japan. However, since no prospective clinical trials comparing high-dose and low-dose statin therapy have been conducted in Asia, we do not know whether high-dose statin therapy could safely improve clinical outcomes in Asian populations. Furthermore, high-intensity statin therapy (e. g. atorvastatin 80 mg) is not covered by Japanese national health insurance, and is thus almost never used.[29] A cross-sectional survey found that in Japan the mean doses of statins are only 1.8 mg for pitavastatin, 3.1 mg for rosuvastatin, and 9.0 mg for atorvastatin.[30] Therefore, 4 mg of pitavastatin is a high dose for Japanese patients. It has been reported that 4 mg of pitavastatin can reduce LDL-C by 42.9% from baseline.[31]

With this as background, we designed and initiated a large-scale, prospective, open-label, multicenter, randomized trial to test whether high-dose statin therapy can reduce the incidence of major cardiovascular events in patients with CAD in Japan.

Methods

Study design and objectives: The REAL-CAD (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease) study (NCT01042730, UMIN000002680) is a prospective, multicenter, randomized, open-label, blinded-endpoint, physician-initiated phase 4 trial designed to investigate whether high-dose statin therapy could reduce CV events in patients with stable CAD as compared with low-dose statin therapy. We hypothesized that aggressive lipid-lowering treatment with pitavastatin 4 mg/day would reduce the incidence of the composite endpoint comprised of CV death, non-fatal myocardial infarction (MI), non-fatal ischemic stroke, and unstable angina requiring emergency hospitalization. The control group received pitavastatin 1 mg/day. Over 2.5 years of follow-up was planned (Figure).

Ethical approval was obtained from the Public Health Research Foundation ethics review committee and the relevant ethics committees at all participating sites. All patients provided written informed consent. The study was conducted in accordance with ethical principals in the Declaration of Helsinki.

Study population and patient selection: Men and women aged 20 to 80 years with clinically evident stable CAD and elevated LDL-C were eligible for this study. CAD was defined as 1) previous ACS, such as acute myocardial infarction or unstable angina; 2) a previous coronary revascularization procedure (PCI or coronary artery bypass grafting [CABG]); or 3) atherosclerotic CAD detected by coronary artery angiography with at least 75% stenosis in major epicardial coronary arteries (American Heart Association classification).[32] Patients with elevated LDL-C at entry were defined as 1) patients not receiving chronic lipid-lowering therapy with LDL-C ≥ 140 mg/dL, 2) patients with LDL-C ≥ 100 mg/dL and considered by the attending physician to need lipid-lowering therapy, or 3) patients being treated with lipid-lowering therapy.

Exclusion criteria included: 1) any planned coronary revascularization procedure, 2) active malignancy, 3) contraindication for pitavastatin (hypersensitivity to pitavastatin, severe liver disease or hepatic dysfunction, concurrent cyclosporin use, or suspected or confirmed pregnancy or current breastfeeding), 4) severe congestive heart failure (ejection fraction < 30% or NYHA class ≥ 3), 5) current hemodialysis, 6) familial hypercholesterolemia, 7) current participation in another clinical trial, 8) current use of any prohibited drug (lipid-lowering drug other than pitavastatin) that could not be discontinued during the study, and 9) any other finding that would make the patient unsuitable for this study in the opinion of the investigators.

Randomization and treatment protocol: Participants were recruited at 733 hospitals in Japan. During screening visits, informed consent and baseline medical history were obtained, and a clinical examination and laboratory testing were performed. Blood samples were collected to determine fasting lipid levels and the patient's standard clinical profile. After discontinuation of all previous lipid-lowering therapies, all eligible patients started receiving treatment with pitavastatin 1 mg/day on an open-label basis for at

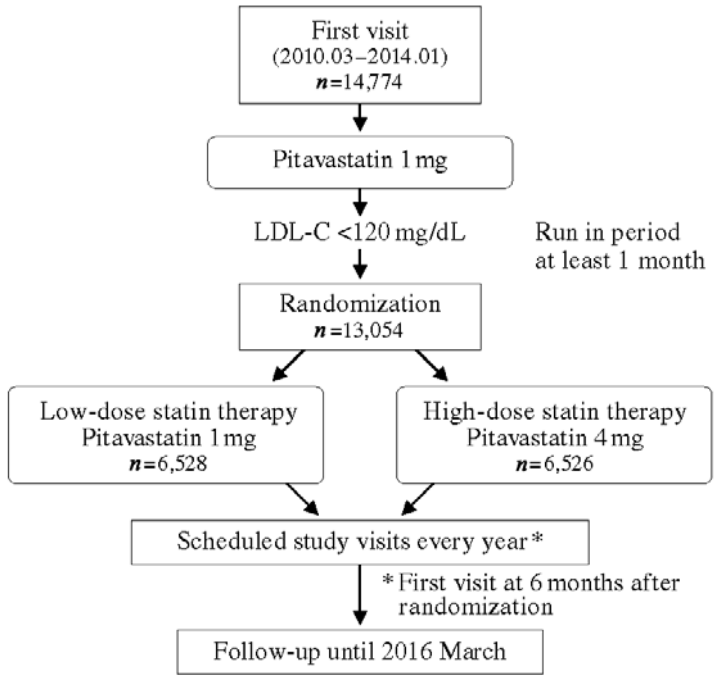

Figure. Summary of study design. LDL-C indicates low-density lipoprotein cholesterol

least 1 month (run-in period). At the end of the run-in period (week 0), those patients with LDL-C levels below 120 mg/dL, measured by a central laboratory using Friedwald's formula, were eligible for randomization. Patients with prior ACS or coronary revascularization could be randomized beyond 3 months after the index event. Randomization was not allowed for patients with poor adherence (less than 50%) for the study drug during the run-in period or for patients with the primary endpoint events during the run-in period.

Patients were randomized in a 1:1 ratio to either pitavastatin 4 mg or pitavastatin 1 mg once daily. Randomized treatment assignment was stratified by 5 factors: 1) institution, 2) prior statin use, 3) age (< 65 or ≥ 65), 4) diabetes, and 5) sex. Patients were to be followed for 3 years, and study visits were scheduled at 6 months for the first visit and every year thereafter. At each visit, information on vital signs, clinical endpoints, adverse events, and concurrent medication was collected. In addition, physical examinations and electrocardiograms were performed and blood specimens were collected at 6 months and every 12 months thereafter for lipid and other laboratory tests.

Endpoints: The primary endpoint of the trial is a composite of CV death, non-fatal MI, non-fatal ischemic stroke, or unstable angina requiring urgent hospitalization. The secondary endpoints include: 1) composite CV events (CV death, non-fatal MI, non-fatal ischemic stroke, unstable angina requiring urgent hospital admission, and coronary revascularization for non-target lesions at previous coronary revascularization), 2) composite coronary events (coronary death, non-fatal MI, unstable angina requiring urgent hospital admission, and coronary revascularization), 3) composite cerebrovascular events (fatal or non-fatal stroke and transient ischemic attack requiring hospital admission), 4) death (all cause death, CV death, cardiac death, death from coronary heart disease [CHD]), 5) individual cardiac events (fatal and non-fatal MI, unstable angina requiring urgent hospital admission, hospitalization with primary diagnosis of congestive heart failure, coronary revascularization, resuscitated cardiac arrest), 6) individual cerebrovascular events (fatal and non-fatal stroke, fatal and non-fatal ischemic stroke, fatal and non-fatal hemorrhagic stroke, and transient ischemic attack requiring hospital admission), and 7) other events (operation or rupture of aortic aneurysms, aortic dissection, revascularization for peripheral artery disease, carotid endarterectomy or stenting, venous thromboembolism, new onset of malignancy, surgery for aortic stenosis).

Statistical design and analysis: Using the data from the J-LIT study, we estimated that a 10-mg/dL reduction in LDL-C would translate to an 8% reduction of CV events.[1] A post marketing survey of pitavastatin found that LDL-C levels in patients treated with 4 mg of pitavastatin were about 20 mg/dL lower than in those treated with 1 mg of pitavastatin.[31] The expected 20 mg/dL difference in LDL-C between the two groups would translate into a 16% CV risk reduction, for a hazard ratio (HR) of 0.84. This estimated HR is consistent with the results from a meta-analysis that reported an odds ratio of 0.84 for composite CV events with aggressive lipid-lowering therapy com-

Table. Baseline Data

Variable	n = 12,413
Age (years)	68.1 ± 8.3
Men (%)	82.6
Height (cm)	162.4 ± 8.1
Body weight (kg)	65.2 ± 11.3
BMI (kg/m^2)	24.6 ± 3.4
Cardiovascular history	
Hospitalization for UA (%)	25.5
Myocardial infarction (%)	51.4
Revascularization	
PCI (%)	83.5
CABG (%)	12.7
Cerebrovascular disease (%)	8.1
Peripheral arterial disease (%)	7.0
Diabetes mellitus (%)	40.1
Current smoker (%)	16.4
Former smoker (%)	49.4
Hypertension (%)	75.7
Family history of CAD (%)	16.5
History of congestive heart failure (%)	5.2
Atrial fibrillation/flutter (%)	6.2
History of malignancy (%)	5.3
Baseline statin use (%)	90.9
Total cholesterol (mg/dL)	166.8 ± 24.3
LDL-C (mg/dL)	87.9 ± 18.9
HDL-C (mg/dL)	50.7 ± 12.6
Triglycerides (mg/dL), median (IQR)	124 (89-174)
hsCRP (mg/L), median (IQR)	0.52 (0.25-1.19)
Glucose (mg/dL)	124.1 ± 40.3
HbA1c (%)	5.86 ± 0.85
Systolic blood pressure (mmHg)	127.6 ± 16.2
Diastolic blood pressure (mmHg)	73.0 ± 10.8
Heart rate	69.5 ± 11.6

BMI indicates body mass index; UA, unstable angina; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; CAD, coronary artery disease; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Apo, apolipoprotein; hsCRP, high sensitivity C-reactive protein; IQR, interquartile range; and HbA1c, hemoglobin A1c.

pared to standard lipid lowering.[20] The annual rate of CV events in the primary endpoint of this study was 2% to 5% in the secondary prevention trials and observational studies in Japan.[1-3,28,33,34] However, follow-up time and investigation methods in the current trial were different from the previous studies. Moreover, event rates have gradually decreased with improved treatment options. Thus, we estimated the annual incidence of CV events to be 2.5% per year. Under these assumptions, we anticipated that 1,033 CV events would be required to detect a 16% relative risk reduction with 80% power with a 2-tailed α of 0.05. With an estimated 10% drop-out/nonadherence rate over the course of the trial, a total of 12,600 patients (6,300 per group) would be required to have 1,033 CV events (3-year registration period and 3-year follow-up period). If the event rate was lower than expected, the Data Safety Monitoring Board (DSMB) could evaluate efficacy data and make recommendations regarding extension of the follow-up period.

The actual event rate for the primary endpoint was lower than anticipated; however, on October 27, 2015, the steering committee decided not to extend the study further despite the original event-driven trial design, because of concerns that further extension would negatively impact the quality of the study.

Study operations: The executive committee consisted of members of the academic leadership of the trial (Appendix). The co-investigators were responsible for the independent drafting and editing of all manuscripts and study analyses presented here. An independent DSMB was selected by the executive committee. The DSMB was comprised of qualified clinical scientists who were not investigators in the study. The independent DSMB periodically evaluated safety and efficacy data and made recommendations regarding continuation or modification of the study or study procedures.

An endpoint committee reviewed all potential primary and secondary endpoint events to adjudicate the endpoint designation. The committee members who performed adjudication of events were independent of the study investigators in the trial. A separate manual of operations fully described the methods to be used by the endpoint committee. Study-specific, data-driven algorithms were used to achieve endpoint consensus. In cases of discordant adjudications of events among the committee members, consensus was to be reached through scheduled conference calls or regular meetings.

Results

Baseline data from the REAL-CAD study: The REAL-CAD population was comprised of patients from 768 institutions. The first patient was recruited in January 2010. Randomizations occurred from April 2010 to July 2013. Of the 14,774 patients who entered the open-label run-in period, 13,054 were randomized to pitavastatin 1 mg or 4 mg (Figure). The randomized patients who withdrew agreement in an early stage and violated entry criteria were excluded. The baseline characteristics of these 12,413 patients are shown in the Table.

Discussion

We cannot apply European and American guidelines directly to Japanese patients because 1) the CV event rate in Japan is lower than in Europe and America, and 2) previous studies in Japan have shown that statin therapy reduced CV events down to target LDL-C levels below 100 mg/dL,[1,12] but further lowering has not been adequately studied. IVUS imaging studies in Japan have documented the value of coronary plaque regression down to LDL-C levels below 70 mg/dL, but those studies are vastly underpowered to determine the effects of such lipid-lowering treatment on clinical outcomes. Accordingly, the value of reducing LDL-C levels substantially below 100 mg/dL in patients with CHD, particularly Asian patients, has not been clearly demonstrated, and Japanese guidelines currently recommend reducing LDL-C only to immediately below 100 mg/dL. No prospective clinical trials have been conducted to determine whether clinical outcomes could be improved by achieving even lower LDL-C levels with high-dose statin. Clearly the clinical significance of ag-

gressive lipid-lowering treatment with statins in Japan must be further evaluated.

Japanese and Western patients tend to respond differently to statin dose; a lower dose in Japanese patients will generally have the same effect as a higher dose in Western patients. As a result, the standard statin doses in Europe and America are considered to be relatively aggressive treatment in Japan. This means that direct comparisons between doses used in CAD patients in Western and Japanese studies may be impossible. However, despite clear differences in dose requirements between Western countries and Japan, it is evident that long-term outcomes may be improved by more intensive treatment in both populations. Further studies in Japanese patients with CAD may be required to determine the optimum treatment regimen for statins in this patient population.

The REAL-CAD study, one of the largest randomized trials to compare high-dose versus low-dose statin therapies, provides pivotal evidence for the role of high-dose statin therapy in secondary CAD prevention in Asian subjects.

Disclosures

Conflicts of interest: This study is registered with ClinicalTrials.gov (NCT01042730) and the University Hospital Medical Information Network clinical trial registry (UMIN 000002680).

Appendix

Executive Adviser: Yasushi Saito, Chiba University

Principal Investigators: Ryozo Nagai, Jichi Medical University, Masunori Matsuzaki, St. Hill Hospital

Co-Principal Investigators: Takeshi Kimura, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine; Hiroaki Shimokawa, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine; Hiroyuki Daida, Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine

Working Members: Satoshi Iimuro, Teikyo Academic Research Center, Teikyo University; Hiroshi Iwata, Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine; Yukio Ozaki, Department of Cardiology, Fujita Health University Hospital, Fujita Health University School of Medicine; Ichiro Sakuma, Caress Sapporo Hokko Memorial Clinic, Yoshihisa Nakagawa, Department of Cardiology, Tenri Hospital; Kiyoshi Hibi, Division of Cardiology, Yokohama City University Medical Center; Takafumi Hiro, Division of Cardiology, Department of Medicine, Nihon University School of Medicine; Yoshihiro Fukumoto, Division of Cardiovascular Medicine, Department of Internal Medicine, Kurume University School of Medicine; Seiji Hokimoto, Department of Cardiovascular Medicine, Kumamoto University Hospital; Katsumi Miyauchi, Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine

Clinical Statistician: Yasuo Ohashi, Department of Integrated Science and Technology for Sustainable Society, Chuo University

Events Judgement Committee: Hiroshi Ito, Department of Cardiovascular Medicine, Okayama University, Graduate School of Medicine; Takao Urabe, Department of Neurology, Juntendo University Urayasu Hospital; Yasushi Okada, Clinical Research Institute and Department of Cerebrovascular Medicine and Neurology, National Hospital Organization Kyushu Medical Center; Kazuo Kitagawa, Department of Neurology, Tokyo Women's Medical University; Kazuo Kimura, Division of Cardiology, Yokohama City University Medical Center; Yasuo Terayama, Division of Neurology and Gerontology, Department of Internal Medicine, School of Medicine, Iwate Medical University; Kazunori Toyoda, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center; Takehiko Nagao, Department of Neurology, Nippon Medical School Tama-Nagayama Hospital; Atsushi Hirayama, Division of Cardiology, Department of Medicine, Nihon University School of Medicine; Masayasu Matsumoto, Japan Community Healthcare Organization, Hoshigaoka Medical Center; Tsutomu Yamazaki, Clinical Research Support Center, the University of Tokyo Hospital; Hiroyoshi Yokoi, Cardiovascular Center, Fukuoka Sanno Hospital; Yutaka Otsuji, The Second Department of Internal Medicine, University of Occupational and Environmental Health, School of Medicine; Jun Takahashi, Department of Cardiovascular Medicine, Tohoku University Graduate School of Medicine

Independent Data Monitoring Committee: Shinichi Oikawa, Diabetes-Lifestyle Disease Center, Japan Anti-Tuberculosis Association Fukujuji Hospital; Kotaro Yokote, Department of Clinical Cell Biology and Medicine, Chiba University Graduate School of Medicine; Satoshi Morita (Independent statistician), Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine

CSP-LD Data Center: Hiroshi Ohtsu, NPO Japan Clinical Research Support Unit (J-CRSU) (From the study start date to March 31, 2016); Tamio Teramoto, Teikyo Academic Research Center, Teikyo University (April 1, 2016 to study completion date)

References

1. Mabuchi H, Kita T, Matsuzaki M, *et al*. Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia and coronary heart disease: secondary prevention cohort study of the Japan Lipid Intervention Trial (J-LIT). Circ J 2002; 66: 1096-100.
2. Japanese Coronary Artery Disease (JCAD) Study Investigators. Current status of the background of patients with coronary artery disease in Japan. Circ J 2006; 70: 1256-62.
3. Yokoyama M, Origasa H, Matsuzaki M, *et al*. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007; 369: 1090-8.
4. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994; 344: 1383-9.
5. Sacks FM, Pfeffer MA, Moye LA, *et al*. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med 1996; 335: 1001-9.
6. West of Scotland Coronary Prevention Study Group. Influence of pravastatin and plasma lipids on clinical events in the West of Scotland Coronary Prevention Study (WOSCOPS). Circulation 1998; 97: 1440-5.
7. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med 1998; 339: 1349-57.
8. Heart Protection Study (HPS) Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin

in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; 360: 7-22.
9. Sever PS, Dahlöf B, Poulter NR, *et al*. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003; 361: 1149-58.
10. Colhoun HM, Betteridge DJ, Durrington PN, *et al*. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet 2004; 364: 685-96.
11. Nakamura H, Arakawa K, Itakura H, *et al*. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomised controlled trial. Lancet 2006; 368: 1155-63.
12. Sakamoto T, Kojima S, Ogawa H, *et al*. Effects of early statin treatment on symptomatic heart failure and ischemic events after acute myocardial infarction in Japanese. Am J Cardiol 2006; 97: 1165-71.
13. Teramoto T, Sasaki J, Ishibashi S, *et al*. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerosis cardiovascular diseases in Japan-2012 version. J Atheroscler Thromb 2012; 20: 517-23.
14. Piepoli MF, Hoes AW, Agewall S, *et al*. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016; 37: 2315-81.
15. Grundy SM, Cleeman JI, Merz CN, *et al*. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004; 110: 227-39.
16. de Lemos JA, Blazing MA, Wiviott SD, *et al*. Early intensive vs a delayed conservative simvastatin strategy in patients with acute coronary syndromes: phase Z of the A to Z trial. JAMA 2004; 292: 1307-16.
17. LaRosa JC, Grundy SM, Waters DD, *et al*. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005; 352: 1425-35.
18. Pedersen TR, Faergeman O, Kastelein JJ, *et al*. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: the IDEAL study: a randomized controlled trial. JAMA 2005; 294: 2437-45.
19. Cannon CP, Braunwald E, McCabe CH, *et al*. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004; 350: 1495-504.
20. Cannon CP, Steinberg BA, Murphy SA, Mega JL, Braunwald E. Meta-analysis of cardiovascular outcomes trials comparing intensive versus moderate statin therapy. J Am Coll Cardiol 2006; 48: 438-45.
21. Josan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. CMAJ 2008; 178: 576-84.
22. Stone NJ, Robinson J, Lichtenstein AH, *et al*. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63: 2889-934.
23. Kaneko H, Yajima J, Oikawa Y, *et al*. Recent characteristics and outcomes of Japanese stable angina pectoris after percutaneous coronary intervention. An observational cohort study using the Shinken Database. Int Heart J 2013; 54: 335-40.
24. Natsuaki M, Furukawa Y, Morimoto T, *et al*. Intensity of statin therapy, achieved low-density lipoprotein cholesterol levels and cardiovascular outcomes in Japanese patients after coronary revascularization. Perspectives from the CREDO-Kyoto registry cohort-2. Circ J 2012; 76: 1369-79.
25. Okazaki S, Yokoyama T, Miyauchi K, *et al*. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTABLISH Study. Circulation 2004; 110: 1061-8.
26. Hiro T, Kimura T, Morimoto T, *et al*. Effect of intensive statin therapy on regression of coronary atherosclerosis in patients with acute coronary syndrome. J Am Coll Cardiol 2009; 54: 293-302.
27. Takayama T, Hiro T, Yamagishi M, *et al*. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). Circ J 2009; 73: 2110-7.
28. Dohi T, Miyauchi K, Okazaki S, *et al*. Plaque regression determined by intravascular ultrasound predicts long-term outcomes of patients with acute coronary syndrome. J Atheroscler Thromb 2011; 18: 231-9.
29. Saito Y, Goto Y, Dane A, Strutt K, Raza A. Randomized dose-response study of rosuvastatin in Japanese patients with hypercholesterolemia. J Atheroscler Thromb 2003; 10: 329-36.
30. Teramoto T, Kashiwagi A, Ishibashi S, Daida H. Cross-sectional survey to assess the status of lipid management in high-risk patients with dyslipidemia: clinical impact of combination therapy with ezetimibe. Curr Ther Res Clin Exp 2012; 73: 1-15.
31. Ose L, Budinski D, Hounslow N, Arneson V. Long-term treatment with pitavastatin is effective and well tolerated by patients with primary hypercholesterolemia or combined dyslipidemia. Atherosclerosis 2010; 210: 202-8.
32. Austen WG, Edwards JE, Frye RL, *et al*. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 1975; 51 (4 Suppl): 5-40.
33. Shihara M, Tsutsui H, Tsuchihashi M, *et al*. In-hospital and one-year outcomes for patients undergoing percutaneous coronary intervention for acute myocardial infarction. Am J Cardiol 2002; 90: 932-6.
34. Furukawa Y, Taniguchi R, Ehara N, *et al*. Better survival with statin administration after revascularization therapy in Japanese patients with coronary artery disease: perspectives from the CREDO-Kyoto registry. Circ J 2008; 72: 1937-45.