J Atheroscler Thromb, 2016; 23: 976-990.
doi: 10.5551/jat.33563

Original Article

Rationale and Design of the Standard Versus Intensive Statin Therapy for Hypercholesterolemic Patients with Diabetic Retinopathy (EMPATHY) Study: a Randomized Controlled Trial

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***Aim*: Hyperlipidemia and diabetic retinopathy increase the risk of cardiovascular disease (CVD). The standard versus intEnsive statin therapy for hypercholesteroleMic Patients with diAbetic retinopaTHY (EMPATHY) study examines whether intensive lipid-lowering therapy is superior to standard therapy in reducing the incidence of cardiovascular events in patients with hyperlipidemia and diabetic retinopathy, but without a history of coronary artery disease.**

***Methods*: Patients who had elevated low-density lipoprotein cholesterol (LDL-C) and diabetic retinopathy without a history of coronary artery disease were eligible for the study. Patients were randomly assigned in a 1:1 ratio to receive intensive or standard therapy. Patients are being treated with monotherapy with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor (statin) for a maximum of 5.5 years to achieve the following LDL-C target: <70 mg/dL for the intensive therapy group or ≥100 and <120 mg/dL for the standard therapy group. The primary endpoint is a composite of incidence of CVD and death from CVD.**

***Results*: Between May 2010 and October 2013, 5,995 patients were assessed for eligibility, and 5,144 were assigned to the study treatment (2,571 and 2,573 in the intensive and standard therapy groups, respectively), and baseline data were analyzed from 5,107 (2,550 in the intensive therapy group and 2,557 in the standard therapy group).**

***Conclusions*: This is the first study assessing the benefits of intensive statin therapy in patients with hypercholesterolemia and diabetic retinopathy in a primary prevention setting. Furthermore, this study evaluates the appropriateness of the treat-to-target approach because all patients are treated to achieve specific LDL-C targets by titrating statin therapy.**

Clinical Trial Registration Number: UMIN000003486.

Key words: Dyslipidemia, Diabetic retinopathy, Hydroxymethylglutaryl-CoA reductase inhibitors, Randomized controlled trial, Primary prevention

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Received: October 13, 2015
Accepted for publication: December 25, 2015

Introduction

Elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for cardiovascular disease (CVD) such as myocardial infarction, angina pectoris, stroke, and peripheral arterial disease. Previous results

of randomized controlled trials have indicated that lipid-lowering therapy with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) is effective for reducing the event rate of CVD in a wide range of individuals[1]. On the basis of these findings, a recent clinical guideline has identified elevated LDL-C as the primary target of lipid-lowering therapy and has recommended several therapeutic approaches[2].

Hyperglycemia is another major risk factor for CVD[3]. The results of observational studies suggest that diabetic patients without previous myocardial infarction have as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction[4, 5]. Elevated LDL-C is a powerful risk factor for coronary artery disease in patients with diabetes mellitus (DM)[6], and the effectiveness of lipid-lowering therapy in this population has been established by meta-analysis of randomized controlled trials[7]. These findings provide a rationale for intensive lipid-lowering therapy in patients who have both hypercholesterolemia and DM, and these high-risk patients have been treated to achieve strict target LDL-C goals[2, 3]. However, previous randomized studies have included only a limited number of patients with DM[7], and the effectiveness of lipid-lowering therapy in such subpopulations has not been completely clarified, particularly in those with diabetic complications.

Diabetic retinopathy is a common chronic microvascular complication of DM[8]. In patients with type 2 DM and retinopathy, the risk of incident coronary heart disease and ischemic stroke is elevated independently of known risk factors[9, 10]. Diabetic retinopathy is strongly associated with all-cause mortality[8]. Therefore, this form of microvascular disease may contribute to the development of CVD. This concept is supported by study results showing that approximately 25% of patients with diabetic retinopathy had significant stenotic coronary artery disease[11]. Based on these findings, diabetic patients with retinopathy may need more intensive therapy than those without retinopathy.

The effectiveness of lipid-lowering therapy in reducing the event rate of CVD has been well established in Japan[12-15], and elevated LDL-C is a powerful risk factor for CVD in patients with DM[16]. However, for primary prevention of CVD in patients with DM, the target level of LDL-C in the Japanese guidelines[17] is not as low as in guidelines in the United States[2, 3]. This suggests that the appropriateness of the Japanese target level should be reconsidered.

Furthermore, the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guideline endorses a paradigm shift in strategies for reducing the events of CVD[18]. This guideline calls for adjusting the intensity of statin therapy based on individual patient risk rather than lowering lipid levels to prespecified targets[18, 19]. It also recommends moderate-intensity statin therapy for primary prevention of CVD in patients with DM 40−75 years of age[18]. These statements in the guideline are derived from the fact that most clinical studies have used fixed-dose regimens, and few studies have investigated the effect of high-intensity statin therapy in a primary prevention setting. However, there is a possibility that more aggressive lipid target levels or high-intensity statin therapy may benefit high-risk patients, particularly those with diabetic retinopathy.

Aim

The standard versus intEnsive statin therapy for hypercholesteroleMic Patients with diAbetic retinopaTHY (EMPATHY) study is currently being conducted to determine whether intensive statin therapy is superior to standard therapy in reducing the incidence of cardiovascular (CV) events in patients with hypercholesterolemia and diabetic retinopathy who have no history of coronary artery disease. In this study, we compare the effectiveness of different target LDL-C levels by titrating statin therapy to achieve specific targets. This article reports the design of the study in detail.

Methods

Study Design and Ethical Considerations

This multicenter, prospective randomized, open-label, blinded-endpoint study is being conducted in Japan in accordance with the Declaration of Helsinki and Japanese ethical guidelines for clinical studies. A total of 769 centers (325 hospitals and 444 clinics) are participating in the study. The protocol was reviewed and approved by the institutional review board of each participating center. All patients provided written informed consent. This study has been underway since May 2010, and patient recruitment ended in October 2013. The study is registered with the University Hospital Medical Information Network clinical trials registry, number UMIN000003486.

Study Population

Table 1 shows the inclusion and exclusion criteria. Patients aged at least 30 years who had no history of coronary artery disease were eligible for the study if they had diabetic retinopathy and elevated LDL-C with or without lipid-lowering therapy.

Treatment

Fig. 1 summarizes the study design. The study

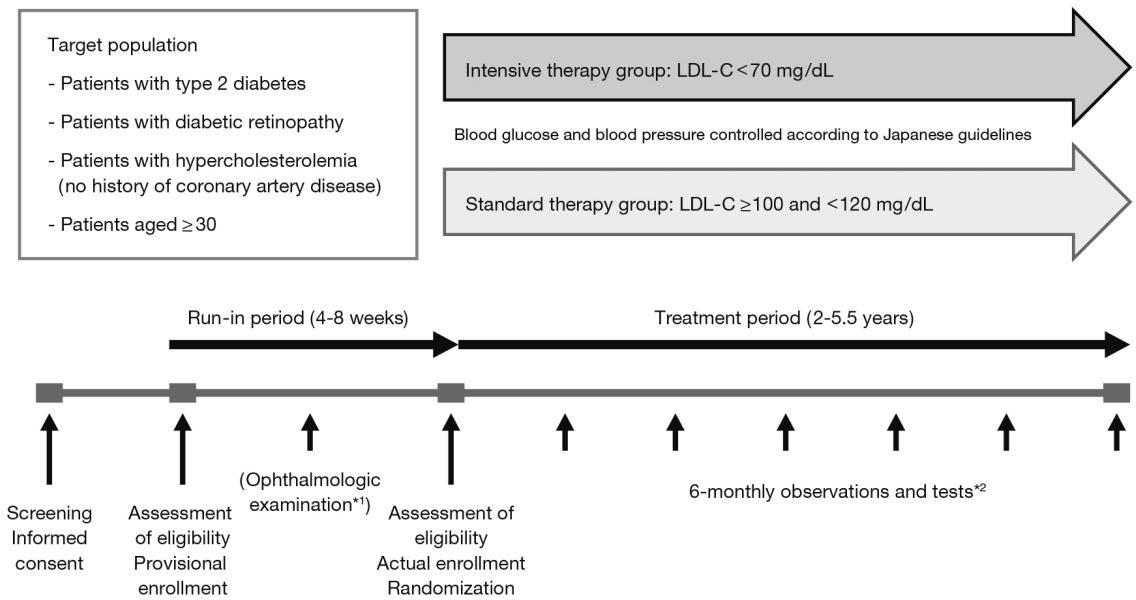
Table 1. Inclusion and exclusion criteria

1) Inclusion criteria
   a) Inclusion criteria for the run-in period
      Patients who meet all of the following criteria are eligible for the run-in period.
      i) Have given written informed consent to participate in this study
      ii) Age at least 30 years (at the time of giving informed consent)
      iii) Man; or woman who not of child-bearing potential during the study
      iv) Outpatient
      v) Hypercholesterolemia with LDL-C[§] ≥ 120 mg/dL for previously untreated patients or ≥ 100 mg/dL for those treated with a single statin[†] or other lipid-lowering drug
      vi) Type 2 diabetes
      vii) No history of CAD (myocardial infarction, angina, or coronary revascularization)
   b) Inclusion criteria for the treatment period
      Patients who meet the inclusion criteria for the run-in period and have documented diabetic retinopathy are eligible for the treatment period.

2) Exclusion criteria
   a) Exclusion criteria for the run-in period
      Patients who meet any of the following criteria are excluded from the study.
      i) History of hypersensitivity to statins
      ii) History of drug-associated muscle disorder
      iii) History of CAD (myocardial infarction, angina, or coronary revascularization)
      iv) History of stroke (including revascularization)
      v) Symptomatic PAD (Fontaine class Ⅱ or higher)
      vi) Uncontrolled hypertension with DBP ≥ 120 mmHg or SBP ≥ 200 mmHg, or hypertensive emergency
      vii) New York Heart Association class ⅡM or higher
      viii) Valvular heart disease with serious hemodynamic abnormality
      ix) Hypercholesterolemia treated with two or more lipid-lowering drugs
      x) Familial hypercholesterolemia
      xi) Serious coexisting illness such as malignant tumor, or severely limited life expectancy (patients are eligible if they received no treatment for at least 5 years and have experiences no relapse of malignancy)
      xii) Renal failure necessitating transplantation or dialysis
      xiii) Patient is pregnant, could be pregnant, or wishes to become pregnant during the study
      xiv) Patient is considered ineligible by the investigator
   b) Exclusion criteria for the treatment period
      Patients who meet any of the following criteria are withdrawn from the study.
      i) Ischemia confirmed by resting electrocardiogram
      ii) Aspartate aminotransferase ≥ 100 IU/L or alanine aminotransferase ≥ 100 IU/L
      iii) Serum creatinine ≥ 2.0 mg/dL or eGFR < 30 mL/min/1.73 m^2
      iv) Nephrotic syndrome
      v) Serum TG ≥ 1000 mg/dL
      vi) Patient is considered ineligible by the investigator

LDL-C, low-density lipoprotein cholesterol; CAD, coronary artery disease; PAD, peripheral artery disease; DBP, diastolic blood pressure; SBP, systolic blood pressure; eGFR, estimated glomerular filtration rate; TG, triglyceride. [§]Values of LDL-C are calculated by the following Friedewald equation; LDL-C = total cholesterol (TC) − [high-density lipoprotein cholesterol (HDL-C) + TG/5] (when TG values are less than 400 mg/dL) or measured by direct homogeneous assay. Values measured within 3 months before obtaining informed consent can be used for assessing eligibility. [†]If patients are treated with atorvastatin, pitavastatin, or rosuvastatin, they should receive no more than the following doses: atorvastatin 10 mg/day, pitavastatin 2 mg/day, rosuvastatin 2.5 mg/day.

consists of a run-in period (4−8 weeks) and a treatment period (2−5.5 years). During the run-in period, patients received statin monotherapy to achieve a target LDL-C level of ≥ 100 and <120 mg/dL and were assessed for eligibility. The diagnosis of diabetic retinopathy was confirmed by an ophthalmologist by the end of the run-in period. Thereafter, eligible patients were randomly assigned in a 1:1 ratio to receive intensive or standard therapy. The allocation sequence was computer generated by a data center and stratified by



*1 Funduscopic data obtained before informed consent can be used. If there is no such data, patients have an ophthalmologic examination during the run-in period.
*2 If the target level of LDL-C is not achieved after six months of study treatment or if LDL-C temporarily reaches the target level, but then rises above or falls below that target level, patients visit hospital every month as a general rule to have lipid tests until achievement of the target is confirmed. If HbA1c is ≥8.4%, patients visit hospital every three months as a general rule to check HbA1c until <8.4% is achieved.

Fig. 1. Summary of the study design

LDL-C, low-density lipoprotein cholesterol; HbA1c, hemoglobin A1c

sex, age (<60 or ≥60 years), and baseline hemoglobin A1c (HbA1c) level (<8.4% or ≥8.4%). If eligibility of the patient was confirmed at the end of the run-in period, the investigator contacted the data center and was notified of the allocated treatment. The person generating the allocation sequence was not involved in patient enrollment.

During the treatment period, patients receive statin monotherapy to achieve an LDL-C target of <70 mg/dL for the intensive therapy group or ≥100 and <120 mg/dL for the standard therapy group. LDL-C levels are calculated from the Friedewald formula. These LDL-C targets are based on guidelines in the United States and Japan, respectively[3, 17]. Statin dose escalation and switching to another statin are permitted in both groups. Individual investigators are permitted to select the statin of their choice as monotherapy, during the run-in and treatment periods.

Concomitant treatment with the following lipid-lowering drugs is prohibited: fibrates, ezetimibe, ethyl icosapentate, anion exchange resins, probucol, nicotinic acid derivatives, phytosterols, elastase, dextran sulfate sodium sulfur, pantethine, and polyenephosphatidylcholine.

Patients are treated with antidiabetic drugs to achieve a target HbA1c level of <6.9% in both groups[20]. They are also treated with antihypertensive drugs to achieve a blood pressure target of <130/80 mmHg[21].

Outcomes

Medical histories, physical examination findings, and laboratory data were obtained for all patients at the beginning of the run-in period. During the treatment period, body weight, blood pressure, pulse rate, and laboratory data are measured every 6 months. Laboratory data include lipids (total cholesterol, LDL-C, high-density lipoprotein cholesterol, triglyceride, apolipoprotein A1, apolipoprotein B, and small dense LDL); HbA1c; glucose; insulin; hematology, hepatic, and renal function tests; serum electrolytes (Na, K, and Cl); creatine kinase; and urinalysis (albumin, creatinine, protein, and urinary sugar). In addition, pleiotropic effects, including antioxidative and anti-inflammatory effects, have been reported to contribute to the effects of statins in treatment to reduce LDL-C[22, 23]. For an auxiliary report of the usefulness of the treatment, explored in this research, brain natriuretic peptide (BNP), high-sensitive C-reactive protein (hsCRP), and high-molecular weight adiponectin are measured every 12 months. Lipid levels, BNP, hsCRP, high-molecular weight adiponectin, and serum creatinine are analyzed at a central laboratory (SRL Inc., Tokyo, Japan). Electrocardiograms are recorded every

Table 2. Primary and secondary endpoints

1) Primary endpoints

The primary endpoint is the combined incidence of cardiovascular events or death associated with cardiovascular events. Cardiovascular events are defined as follows.

a) Cardiac events: myocardial infarction, unstable angina requiring unscheduled hospitalization, or coronary revascularization (percutaneous coronary intervention or coronary artery bypass grafting)

b) Cerebral events: ischemic stroke or cerebral revascularization

c) Renal events: initiation of chronic dialysis, increase in serum creatinine level by at least 2-fold (and >1.5 mg/dL)

d) Vascular events: aortic disease or PAD (aortic dissection, mesenteric artery thrombosis, severe lower limb ischemia [ulceration], revascularization, or finger/lower limb amputation caused by arteriosclerosis obliterans)

2) Secondary endpoints

The secondary endpoints are defined as follows.

a) Death from any cause

b) Individual incidence of cardiac, cerebral, renal or vascular event as defined for the primary endpoint

c) Incidence of stroke (ischemic stroke, hemorrhagic stroke, subarachnoid hemorrhage)

d) Change in laboratory variables related to chronic kidney disease (eGFR, urinary albumin, or urinary protein)

e) Safety

PAD, peripheral artery disease; eGFR, estimated glomerular filtration rate

6 months. Funduscopy is performed every 12 months. Statin treatment compliance, concomitant use of other drugs, and adverse events are periodically investigated throughout the study.

The study endpoints are shown in **Table 2**. The primary endpoint is defined as a composite of incidence of CVD and death from CVD. Most of the previous large-scale clinical studies of statins have used coronary artery disease and stroke as primary endpoints. However, beginning in the 2000s, there has been increasing recognition of the concept of chronic kidney disease (CKD), and a growing understanding that ischemic heart disease, cerebrovascular disease, peripheral vascular disease, and renal impairment are ischemic conditions stemming from arteriosclerosis, and that these conditions are associated with each other. Based on this growing understanding, we set a wider range of primary endpoints of such pathologies based on arteriosclerosis. This range included renal events, which are rarely used in composite endpoints. The clinical significance of establishing the necessity of lipid control in terms of the onset and progression of renal events is based on the findings of a meta-analysis of randomized control and crossover studies of statins, which showed inhibition of proteinuria and mild inhibition of progression of nephropathy[24]. Similar findings have also been reported in Japanese patients[25]. The secondary endpoints are defined as follows: all-cause mortality; occurrence of cardiac, cerebral, renal, and vascular events; occurrence of stroke; prespecified changes in laboratory variables associated with CKD; and safety (adverse events and adverse drug reactions). Primary and secondary endpoints are adjudicated by an event evaluation committee whose members are unaware of the treatment allocation. Definition of events and items assessed for safety are listed in **Tables 3** and **4**.

Discontinuation or Suspension of the Entire Study

The principal investigators will examine the feasibility of continuation of the study if any of the following situations are encountered: (1) Important safety or efficacy information associated with the study is obtained. (2) On the basis of the results of the interim analysis, the Independent Data Monitoring Committee deems that the study has achieved its objective(s) prior to the scheduled number of subjects being reached or completion of the scheduled study period. (3) If changes to the protocol, as specified by the Independent Data Monitoring Committee, are difficult to accommodate. If the Independent Data Monitoring Committee recommends or requires that the study be discontinued, the principal investigators will discontinue the study. In the event that the principal investigators decide to discontinue or suspend the study, the principal investigators will promptly communicate that fact and the reason for suspension in writing to the heads of the participating test sites.

Quality Management

During the study, the participating institutions and investigators are periodically monitored by contract research organizations. In addition, a prespecified proportion of the institutions is scheduled to undergo data audit including direct access to source data. This study is conducted under contract among the follow-

Table 3. Definitions of endpoints

1) Myocardial infarction

Myocardial infarction is defined as an increase in cardiac biomarkers (preferably troponin or, if unavailable, CK-MB), as well as any one of the following:

• Chest pain

• New ischemic ECG changes

• Loss of myocardial viability or the presence of wall motion abnormality on imaging

If more than 30 days has elapsed since onset, evidence of any of the following:

• New pathological Q wave on ECG

• New myocardial thinning, loss of myocardial viability, and contractile dysfunction on imaging

If pathological findings indicate the occurrence of new myocardial infarction, that occurrence will be considered to satisfy the myocardial infarction endpoint.

2) Unstable angina requiring unscheduled hospital admission

Unstable angina requiring unscheduled hospital admission is defined as the occurrence of either typical chest pains or new ischemic ECG changes, in combination with significant stenotic lesions on coronary angiogram (or filling defect evident on scintigram, if coronary angiography is not possible). This is equivalent to severity class Ⅱ or Ⅲ and clinical circumstances class B under the Braunwald classification of unstable angina (1989).

3) Coronary arterial revascularization (percutaneous coronary intervention, coronary artery bypass grafting)

All revascularizations by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) will be included, unless already scheduled at the time of acquisition of informed consent. Such prescheduled procedures will be excluded from consideration.

4) Cerebral infarction

Cerebral infarction is clinically defined as new local neurological symptoms with appropriate lesions confirmed on CT or MRI (MRA).

5) Cerebral hemorrhage

Cerebral hemorrhage is clinically defined as new-onset local neurological symptoms with fresh hematoma in the cerebrum, cerebellum, and/or brain stem evident on MRI/CT scans of the head. Cerebral hemorrhage does not include cerebral infarction.

6) Subarachnoid hemorrhage

Onset is characterized by sudden headache and disturbed consciousness with bleeding and hematoma in the subarachnoid cavity or blood-stained cerebrospinal fluid evident on MRI/CT scans of the head.

7) Cerebrovascular reconstruction

Carotid endarterectomy, percutaneous transluminal angioplasty, stenting, bypass surgery, unless already scheduled at the time of acquisition of informed consent. Such prescheduled procedures will be excluded from consideration.

8) Permanent dialysis

Patients who require permanent dialysis, unless the introduction of dialysis is clearly due to other diseases (chronic glomerulonephritis, etc.); such dialysis due to other diseases will be excluded from consideration.

9) Serum creatinine increased ≥ 2-fold

Serum creatinine >1.5 mg/dL with increase ≥ 2-fold above the value at registration, as measured in verified testing at onset or within 6 months after onset, and results from hematology and urinalysis rule out other disease (heart failure, bladder cancer, renal calculus, infection, etc.)

10) Large artery disease or peripheral arterial disease (aortic dissection, mesenteric artery thrombosis, occurrence of critical lower limb ischemia [ulcers], revascularization or amputation of digit or lower limb due to obstructive arteriosclerosis)

Aortic dissection: Refers to evidence of aortic splitting on imaging (transesophageal echocardiogram, CT, MRI/MRA, etc.).

Mesenteric artery thrombosis: Refers to evidence of ischemic findings in the superior mesenteric artery (mainly the origin of the artery) on abdominal ultrasound, CT, or angiogram.

Occurrence of critical lower limb ischemia [ulcers] due to obstructive arteriosclerosis, revascularization or amputation of digit or lower limb will refer to the occurrence of any of the following: Critical lower limb ischemia (Fontaine grade Ⅳ) with ulceration due to obstructive arteriosclerosis, revascularization (percutaneous transluminal angioplasty, bypass grafting), or amputation of digit or lower limb.

11) Death: To be confirmed by death certificate if at all possible.

Death due to events: This category includes death due to events stipulated by endpoints in the study protocol. However, deaths will be excluded if other clear causes are identified in the relationship between the death and the event.

Total mortality: All deaths will be included. The cause of death, if other than death due to events, will be identified wherever possible.

Table 4. Definitions related to adverse events

1) Definition of an adverse event

An adverse event is defined as follows.

An "adverse event" is defined as "any unfavorable medical event experienced by a patient or subject receiving a drug. It does not necessarily refer only to those events for which there is a clear causal relationship with the said drug. Briefly, an adverse event means any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease associated with the use of a drug that may or may not be considered related to, or caused by, the drug."

Developments such as a change in blood glucose, etc., aggravation of diabetes mellitus, or a change in serum lipid levels associated with the target disease (diabetic retinopathy complicated by hypercholesterolemia) do not constitute adverse events unless the change is excessive and contraindicates continuation of the study. In addition, if abnormal changes in laboratory findings, vital signs, or ECG results associated with signs, symptoms, or disease are observed, the sign, symptom, or disease will be reported as an adverse event. Laboratory findings outside the range specified in the Study Protocol will be reported as additional information regarding the adverse event.

2) Definition of a serious adverse event

Those adverse events that satisfy any of the following definitions will be regarded as "serious adverse events."

a) Events resulting in death

b) Events that are life-threatening

c) Events requiring hospitalization or prolongation of existing hospitalization for treatment

d) Events resulting in a permanent or significant disability/incapacity

e) Events resulting in a congenital abnormality

f) Events or reactions resulting in another medically significant condition

f) refers to medically significant events or reactions that may put patients at risk and require action or treatment to prevent an outcome such as those described in a) to e), even if they are not immediately life-threatening or do not result in death or hospital admission.

3) Definition of an adverse reaction

All adverse events other than those classified as "not related" to statin therapy will be handled as adverse reactions due to statin therapy.

If an adverse event occurs, the investigator will record the name of the adverse event, date of onset, severity, seriousness/non-seriousness, changes (if any) in statin therapy, changes (if any) in treatment with drugs other than statin, outcome and date outcome confirmed, causal relationship with statin, and causal relationship with concomitant drugs. The survey of adverse events will be performed during the observation period and the study treatment period.

ing organizations: the funder (Shionogi & Co., Ltd. Osaka, Japan), participating institutions, and the contract research organizations.

Statistical Considerations

A sample size of 5,000 patients (2,500 in each group) was selected to detect the superiority of intensive therapy with a power of 80% and a two-sided significance level of 5%. Based on earlier reports in the literature[26-29], we estimated that the incidence of CV events during the 3-year treatment period would be 4.1% and 2.7% for the standard and intensive therapy groups, respectively. The sample size was chosen based on these estimates, assuming a withdrawal rate of 15%, and a study period of 4.5 years was selected.

The main analysis set for efficacy will be the full analysis set (FAS). For primary and secondary endpoints, the same analysis will be performed in the per-protocol set (PPS) as in FAS, and the consistency of results for the two sets will be examined. FAS will consist of all randomly allocated subjects except for those for whom efficacy endpoints were not observed. PPS will consist of FAS less nonqualifying cases, untreated cases, protocol violations, and noncompliance cases. The safety analysis set will consist of those subjects who receive the study treatment at least once and from whom any information pertaining to safety is obtained. In all analyses, each subject will be included in the allocation group.

A log-rank test, stratified by sex, age, and baseline HbA1c, will be used to compare the primary endpoint between the treatment groups. The hazard ratio and its 95% confidence interval will be estimated using the stratified Cox proportional hazards model. During the study, an interim analysis is planned once at a prespecified time point adjusted by the Lan-DeMets α spending function with O'Brien-Fleming boundaries. Results of the interim analysis are to be assessed by an Independent Data Monitoring Committee.

Results

Fig. 2 shows a flow chart of the study patients.

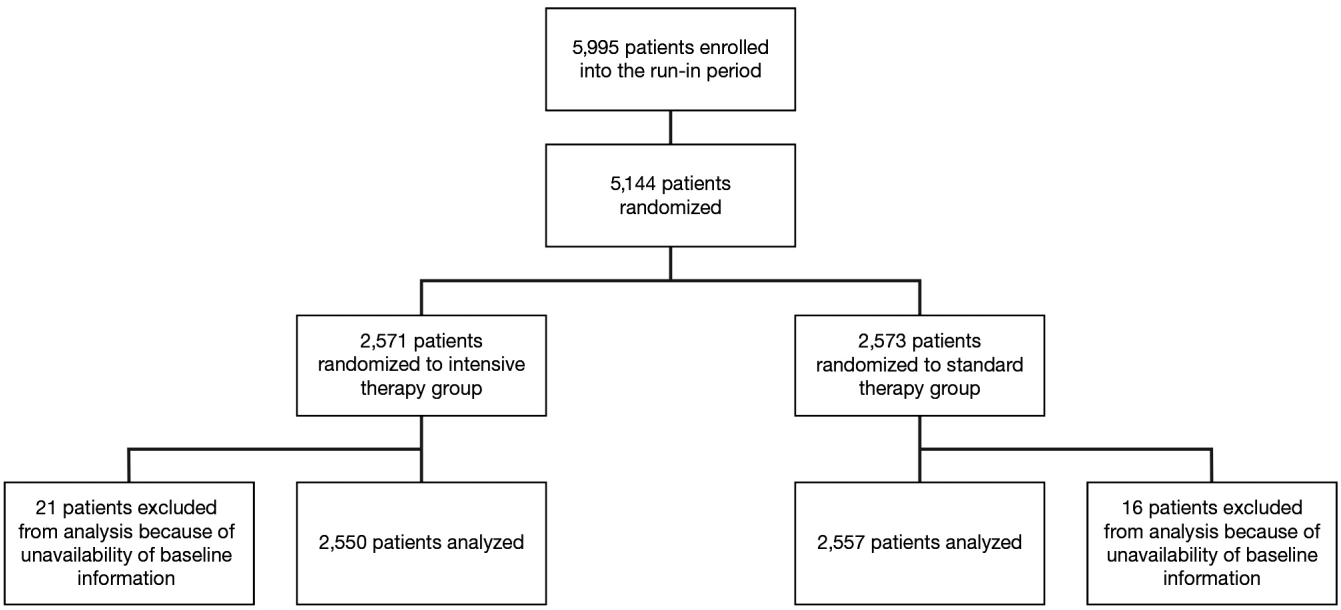


Fig. 2. Flow chart of the study patients

Between May 2010 and October 2013, 5,995 patients were enrolled into the run-in period, and 5,144 patients were randomized to treatment (2,571 to the intensive therapy group and 2,573 to the standard therapy group). Of that number, 37 were excluded from analysis because of unavailability of baseline information; reasons included data loss due to the major earthquake in eastern Japan in March 2011, major deviations from study ethics, and withdrawal of patient consent. The analysis population was thus 5,107 patients (2,550 in the intensive therapy group and 2,557 in the standard therapy group).

The baseline characteristics of the patients enrolled into the treatment period are shown in **Table 5**. The baseline characteristics were well balanced between the treatment groups. Mean LDL-C levels decreased from the run-in period to the beginning of the treatment period in both groups. Retinopathic complications were present in less than 100% of subjects because 20 subjects had previously undergone laser therapy for retinopathy and 8 subjects were erroneously registered as having retinopathy at the time of enrollment. Those patients were included in the FAS analysis.

Discussion and Conclusion

We are conducting this study to determine whether intensive statin therapy is superior to standard therapy in reducing CV events in patients who have hypercholesterolemia and diabetic retinopathy in a primary prevention setting.

Although the risk of CV events is as high in diabetic patients with no previous history of CV events as in nondiabetic patients with previous myocardial infarction[4, 5], few studies have investigated the benefits of intensive statin therapy for the primary prevention of CVD in these high-risk patients, especially those with diabetic complications. In previous randomized controlled trials that assessed the benefits of intensive therapy, only a limited proportion of patients with DM were included, and the studies assessed the benefits of statins in secondary prevention[30-34]. Thus, the benefits of intensive therapy for primary prevention in high-risk patients remain poorly elucidated. It may be desirable to reconsider the currently recommended lipid-lowering targets in Japan, in light of international recommendations based on the study results described above.

There is also clear evidence that diabetic patients with retinopathy have a higher risk of CVD than those without retinopathy. In the previous cohort studies in patients with type 2 DM, the presence of diabetic retinopathy was associated with a higher risk of incident coronary heart disease and ischemic stroke[9, 10]. To our knowledge, however, no studies have assessed the effectiveness of statin therapy in this subpopulation. Our results will add new findings to the existing data, because approximately 5,000 patients with diabetic retinopathy will be followed for 2−5.5 years.

In our study, we treat all patients to achieve specific LDL-C targets by titrating statin therapy instead of using fixed-dose regimens. In other words, we aim

Table 5. Baseline characteristics

	Intensive therapy group (n = 2,550) n (%)	Standard therapy group (n = 2,557) n (%)
Sex, Male	1,213 (47.6%)	1,219 (47.7%)
Age (mean ± SD)	63.0 ± 10.8	63.2 ± 10.4
Body mass index (kg/m^2) (mean ± SD)	25.69 ± 4.25	25.59 ± 4.36
Anti-hyperlipidemia medicine [§]		
None	1,122 (44.0%)	1,053 (41.2%)
One drug	1,421 (55.7%)	1,501 (58.7%)
Two drugs	7 (0.3%)	3 (0.1%)
Smoking [†]	465 (18.2%)	490 (19.2%)
Family history of CAD	326 (12.8%)	318 (12.4%)
Family history of cerebrovascular disease	497 (19.5%)	531 (20.8%)
Duration of diabetes (yr, mean ± SD)	12.8 ± 8.6	13.0 ± 9.0
Diabetic complication		
Retinopathy	2,543 (99.7%)	2,546 (99.6%)
Neuropathy	756 (29.6%)	764 (29.9%)
Nephropathy	1,320 (51.8%)	1,270 (49.7%)
Hypertension	1,769 (69.4%)	1,791 (70.0%)
PAD	117 (4.6%)	98 (3.8%)
Funduscopy		
Simple retinopathy	1,706 (66.9%)	1,692 (66.2%)
Preproliferative retinopathy	424 (16.6%)	480 (18.8%)
Proliferative retinopathy	396 (15.5%)	368 (14.4%)
Hemoglobin A1c (%) [‡] [mean ± SD (n)]	7.77 ± 1.27 (2,550)	7.77 ± 1.25 (2,557)
LDL-C (mg/dL) [‖] [mean ± SD (n)]		
Beginning of the run-in period [§§]		
Patients who had not received lipid-lowering therapy previously	143.1 ± 23.5 (714)	140.4 ± 22.9 (666)
Patients who had received previous therapy	120.5 ± 22.1 (917)	120.9 ± 23.5 (958)
Beginning of the treatment period		
Patients who had not received lipid-lowering therapy previously	98.4 ± 25.8 (1,101)	97.7 ± 24.6 (1,033)
Patients who had received previous therapy	112.3 ± 25.8 (1,398)	112.0 ± 25.0 (1,460)
All	106.2 ± 26.7 (2,499)	106.0 ± 25.8 (2,493)
SBP (mmHg) [††] [mean ± SD (n)]	134.7 ± 16.9 (2,526)	134.5 ± 16.2 (2,536)
DBP (mmHg) [††] [mean ± SD (n)]	74.9 ± 11.6 (2,526)	74.7 ± 11.1 (2,536)

CAD, coronary artery disease; PAD, peripheral artery disease; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure. [§]Values were calculated at the beginning of the run-in period. [†]The categories of "Past Smoker" and "Non Smoker" were combined as "Not Current Smoker." [‡]Values were calculated at the time of consent. [‖]Values were calculated using the Friedewald equation; LDL-C = total cholesterol (TC) − [high-density lipoprotein cholesterol (HDL-C) + triglyceride (TG)/5]. [§§]Values were measured at each study center. Only data obtained by the Friedewald equation were used for totaling. [††]Values were calculated at the beginning of the treatment.

to compare the effectiveness of different LDL-C targets. Recently, the 2013 ACC/AHA Task Force Guideline was unable to find evidence to support titrating statin therapy to achieve LDL-C targets, because most clinical studies confirming the effectiveness of statins have used fixed-dose regimens[18]. However, the treat-to-target approach was recommended in a guideline from the Adult Treatment Panel III[2] and a related Japanese guideline also adopted this approach[17]. Under these circumstances, it is worthwhile to conduct a clinical study to determine the appropriateness of the treat-to-target approach.

To ensure the reliability of study records, a prespecified proportion of the institutions are scheduled to undergo data audit including direct access to source data. Although data audit should be conducted in all interventional clinical trials, it has been omitted in some Japanese clinical trials except for those aimed at new drug applications. Especially in large-scale, long-term trials in patients with chronic disease, data audit

has seldom been scheduled. Thus, our results may also give some insights into the quality of clinical trials in Japan.

Within the category of baseline characteristics, mean LDL-C levels decreased during the run-in period in both groups.

In conclusion, this is the first study assessing the benefits of intensive statin therapy in patients with hypercholesterolemia and diabetic retinopathy who do not have a history of coronary artery disease. It also evaluates the appropriateness of the treat-to-target approach by titrating statin therapy to achieve specific LDL-C targets.

Acknowledgements

The study is funded by Shionogi & Co., Ltd. Shionogi & Co., Ltd. does not participate in data collection or event evaluation, does not have data access rights, and does not play a role in statistical analysis. The principal investigators and members of the Protocol Committee designed the study in collaboration with Shionogi & Co., Ltd. EDIT, Inc. (Tokyo, Japan) provided medical writing and editing. The authors had final responsibility for the decision to submit for publication.

Disclosure

Kenji Ueshima reports honoraria from Shionogi & Co., Ltd., Pfizer Japan Inc. and Astellas Pharma Inc., and research funding from Pfizer Japan Inc., Daiichi Sankyo Co., Ltd. and Chugai Pharmaceutical Co., Ltd. Hiroshi Itoh reports advisory role of Nipro Corporation and SBI Pharmaceuticals Co., Ltd., honoraria from Takeda Pharmaceutical Co., Ltd., MSD K.K., Novartis Pharma K.K., Daiichi Sankyo Co., Ltd., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc., Astellas Pharma Inc. and Shionogi & Co., Ltd., and research funding from Mitsubishi Tanabe Pharma Corporation, MSD K.K., Daiichi Sankyo Co., Ltd., Astellas Pharma Inc., Kyowa Hakko Kirin Co., Ltd., AstraZeneca K.K., Eli Lilly Japan K.K., Sanofi K.K., Teijin Pharma Ltd., Mochida Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Pfizer Japan Inc., Johnson & Johnson K.K., Torii Pharmaceutical Co., Ltd. and Bristol-Myers Squibb Company. Nobuaki Kanazawa reports employment of Shionogi & Co., Ltd. Issei Komuro reports honoraria from Takeda Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Mitsubishi Tanabe Pharma Corporation and Daiichi Sankyo Co., Ltd., and research funding from Takeda Pharmaceutical Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Astellas Pharma Inc., Daiichi Sankyo Co., Ltd., Genzyme Japan K.K., Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc., MSD K.K., GlaxoSmithKline K.K., Sanofi K.K., Sumitomo Dainippon Pharma Co., Ltd., Novartis Pharma K.K., Otsuka Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., AstraZeneca K.K., Bayer Yakuhin, Ltd., Teijin Pharma Ltd., Chugai Pharmaceutical Co., Ltd., Kowa Pharmaceutical Co., Ltd., Actelion Pharmaceuticals Japan Ltd., Taisho Toyama Pharmaceutical Co., Ltd. and Bristol-Myers Squibb Company. Ryozo Nagai reports honoraria from Mitsubishi Tanabe Pharma Corporation, Kowa Pharmaceutical Co., Ltd., Shionogi & Co., Ltd. and Nippon Boehringer Ingelheim Co., Ltd. Masahiro Takeuchi reports honoraria from Hisamitsu Pharmaceutical Co., Inc., AstraZeneca K.K., Taiho Pharmaceutical Co., Ltd., Shionogi & Co., Ltd. and Kowa Pharmaceutical Co., Ltd. Tsutomu Yamazaki reports honoraria from Takeda Pharmaceutical Co., Ltd., Shionogi & Co., Ltd., AstraZeneca K.K. and Sumitomo Dainippon Pharma Co., Ltd.

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Appendix

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Saito; Shumpei Saito; Setsuya Sakagashira; Daisuke Sakaguchi; Ichiro Sakaguchi; Eiji Sakai; Naoshi Sakai; Noriko Sakamoto; Koichiro Sakota; Ichiro Sakuma; Kenichi Sakurai; Shunichiro Sakurai; Hisako Sameshima; Akira Sanada; Yutaka Sasagawa; Hiromitsu Sasaki; Iwao Sasaki; Takashi Sasaki; Masataka Sata; Atsushi Sato; Kazutoshi Sato; Koichi Sato; Koichiro Sato; Naoichi Sato; Nobuyuki Sato; Takako Sato; Tatsuyuki Sato; Ken Sawada; Tadashi Sawada; Kimikazu Sawai; Hideaki Sawaki; Yoshitaka Sayo; Ikuo Segawa; Tadashi Seguchi; Hiroaki Seino; Naoto Seki; Taiji Sekigami; Naotaka Sekiguchi; Syunji Sekiguchi; Nobuo Sekine; Risa Sekioka; Nobuko Sera; Yasunori Sera; Osamu Seto; Kozo Shaura; Masaaki Shibamoto; Hirotaka Shibata; Toshiro Shibata; Makoto Shibuya; Ryutaro Shigeta; Takao Shimada; Ryuji Shimamura; Ikki Shimizu; Kazuhiko Shimizu; Masashi Shimizu; Mitsuo Shimizu; Satoshi Shimizu; Masashi Shimoda; Shigeto Shimoda; Yoshio Shindo; Kouichiro Shiojima; Toshihiko Shiraiwa; Takuhiro Shirakawa; Nobuhiro Shiroyama; Yoshihito Shoda; Tetsuo Shoji; Hirohisa Shono; Hiroshi Shuto; Satoshi Soda; Kuninori Soejima; Shoichi Suemori; Minoru Suezawa; Muneki Sugata; Tatsushi Sugiura; Toru Sugiyama; Yasuhiro Sumida; Hiroshi Sunagawa; Katsuo Suyama; Hitoshi Suzuki; Susumu Suzuki; Takanori Suzuki; Tsunehito Suzuki; Haruyuki Taguchi; Shigeru Tai; Tsuyoshi Taira; Ichitaro Takada; Yoshihisa Takada; Junko Takagi; Shuichi Takagi; Yusuke Takagi; Kazuko Takahashi; Kazunori Takahashi; Kenro Takahashi; Kiyoshi Takahashi; Nobuo Takahashi; Shunsuke Takahashi; Soichiro Takahashi; Tadayoshi Takahashi; Toru Takahasi; Masato Takaki; Ichiro Takamura; Toshinari Takamura; Noriyuki Takano; Tatsuro Takano; Ken Takao; Taizo Takase; Hiroshi Takeda; Tomoo Takeda; Masanori Takeishi; Kiyoshi Takekawa; Yuji Takemoto; Ken Takenaka; Naohide Takeuchi; Yasuo Takeuchi; Hirofumi Takino; Toru Tamai; Kazuhiro Tamaki; Noboru Tamaki; Toshio Tamaki; Hideki Tamura; Hiroyuki Tamura; Yukihiro Tamura; Akihiko Tanaka; Hideki Tanaka; Hiroaki Tanaka; Kenji Tanaka; Masayuki Tanaka; Toru Tanaka; Toru Tanaka; Tsuyoshi Tanaka; Yasushi Tanaka; Makio Tani; Ken Tanigawa; Masato Taniguchi; Matsuo Taniyama; Toshihiro Tanzawa; Eiji Tatsumi; Noriyasu Taya; Jin Temma; Shouji Terada; Yasushi Terada; Yoshio Terada; Naoki Tezuka; Hisako Toda; Haruhiko Tokuda; Eiichi Tokutake; Kenichi Tokuyama; Takahiko Tokuyama; Katsuyuki Tome; Naruya Tomita; Yukio Tone; Rieko Totani; Jo Toyota; Tetsuo Tsubone; Akihito Tsuchida; Atsushi Tsuchiya; Hiroaki Tsuchiya; Norihiro Tsuchiya; Masahiro Tsuji; Motoyoshi Tsujino; Kazuhisa Tsukamoto; Taku Tsunekawa; Masatoshi Tsuru; Masahiro Tsutsui; Akihito Tsutsumi; Sachie Tsuzura; Daigaku Uchida; Yasuko Uchigata; Kazuaki Uchiyama; Hiroo Ueda; Junichi Ueda; Kazuya Ueda; Naohiko Ueda; Nobuyuki Ueda; Yasuo Ueda; Koichiro Uehara; Hiroaki Ueno; Makoto Ujihara; Fumio Umeda; Nobuo Uno; Satoshi Uramoto; Toshihiko Urushibara; Yoshihide Ushitani; Mikiya Usukura; Satoko Wada; Yutaka Wakasa; Takanobu Wakasugi; Masako Waki; Genichi Watanabe; Hitoshi Watanabe; Ikuo Watanabe; Masayuki Watanabe; Ryouichiro Watanabe; Yoshiyuki Watanabe; Matahiro Yabuta; Ken Yaga; Kunimasa Yagi; Kenji Yaginuma; Ryuichiro Yagyu; Hiroharu Yamada; Kenji Yamada; Masayo Yamada; Mitsutoshi Yamada; Satoru Yamada; Shoichi Yamada; Tetsuhiro Yamada; Tsutomu Yamada; Yoshihiko Yamada; Shigeru Yamaga; Toshiharu Yamagata; Toru Yamaguchi; Kouzaburo Yamaji; Chifumi Yamamoto; Hidefumi Yamamoto; Kenichi Yamamoto; Koji Yamamoto; Manabu Yamamoto; Yoshikazu Yamamoto; Ritsuko Yamamoto-Honda; Hidetoshi Yamashita; Iwao Yamashita; Shigeo Yamashita; Tetsuji Yamashita; Kazuhiko Yamauchi; Kenji Yamauchi; Yuichiro Yamauchi; Seiichi Yamawaki; Jun Yan; Tatsuo Yanagawa; Katsuyuki Yanagisawa; Masatoshi Yanagisawa; Toshihiko Yanase; Harumi Yano; Mayumi Yano; Yutaka Yano; Hideki Yasuda; Koichiro Yasuda; Takahiro Yazu; Mineto Yokoi; Tamotsu Yokota; Akihiro Yokoyama; Kazunori Yokoyama; Hidetada Yoshida; Katsumi Yoshida; Kenichi Yoshida; Masanori Yoshida; Tomoki Yoshida; Toshimi Yoshida; Naomi Yoshimura; Mototaka Yoshinari; Gen Yoshino; Munenori Yoshizumi; Atsuyoshi Yuhara; Masakatsu Yuito; Yasuo Yumori.