Study Profile

Rationale and Design of the PROSPECTIVE Trial: Probucol Trial for Secondary Prevention of Atherosclerotic Events in Patients with Prior Coronary Heart Disease

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Background: Reduction of serum LDL-cholesterol by statins was shown to improve clinical outcomes in patients with coronary heart disease (CHD). Although intensive statin therapy significantly reduced cardiovascular risks, atherosclerotic cardiovascular events have not been completely prevented. Therefore, effective pharmacologic therapy is necessary to improve “residual risks” in combination with statins. Probucol has a potent antioxidative effect, inhibits the oxidation of LDL, and reduces xanthomas. Probucol Trial for Secondary Prevention of Atherosclerotic Events in Patients with Prior Coronary Heart Disease (PROSPECTIVE) is a multicenter, randomized, prospective study designed to test the hypothesis that the addition of probucol to other lipid-lowering drugs will prevent cerebro- and cardiovascular events in patients with prior coronary events and high LDL cholesterol levels.

Study Design: The study will recruit approximately 860 patients with a prior CHD and dyslipidemia with LDL-C level ≥140 mg/dl without any medication and those treated with any lipid-lowering drugs with LDL-C level ≥100 mg/dl. Lipid-lowering agents are continuously administered during the study period in control group, and probucol (500 mg/day, 250 mg twice daily) is added to lipid-lowering therapy in the test group. The efficacy and safety of probucol with regard to the prevention of cerebro- and cardiovascular events and the intima-media thickness of carotid arteries as a surrogate marker will be evaluated.

Summary: PROSPECTIVE will determine whether the addition of probucol to other lipid-lowering drugs improves cerebro- and cardiovascular outcomes in patients with prior coronary heart disease. Furthermore, the safety of a long-term treatment with probucol will be clarified.


Key words: Probucol, Lipid lowering therapy, Coronary heart disease, Prevention

Background

The main purpose of dyslipidemia treatment is to prevent atherosclerotic cerebrovascular and cardiovascular events and to improve the mortality correlated with these events. As stated in the Japanese Ath-
elevated cholesterol transport from atheromatous plaques to the liver, resulting in the significant regression of xanthelasmas and Achilles tendon xanthomas in patients with familial hypercholesterolemia (FH). Various clinical results indicating the efficacy of probucol for preventing atherosclerotic cardiovascular disease have been reported; probucol improved the long-term prognosis and secondary prevention in patients with heterozygous FH, reduced restenosis and the revascularization rate after percutaneous coronary intervention (PCI), and improved endothelium-dependent coronary vasomotion and common carotid atherosclerosis in patients with hypercholesterolemia. However, the effect of probucol on preventing atherosclerotic cerebro- and cardiovascular events has not been proven in a long-term, large-scale, double-blind study. Recently, we examined a retrospective observational study with regard to the cerebro- and cardioprotective effects of probucol in patients with heterozygous FH. The study cohort included 410 patients with heterozygous FH, diagnosed between 1984 and 1999 by cardiovascular and metabolic experts at 15 centers. After possible confounding factors were adjusted, probucol significantly decreased the risk for cerebro- and cardiovascular events (hazard ratio [HR], 0.13; 95% confidence interval [CI], 0.05–0.34) in secondary prevention (p < 0.001). However, it is unknown whether the probucol therapy combined with statins will provide further clinical benefit in secondary prevention in patients with dyslipidemia other than FH.

Therefore, in the current randomized prospective study, we plan to evaluate the safety and efficacy of probucol in addition to other lipid-lowering drugs for the prevention of cerebro- and cardiovascular events in patients with prior coronary events and high LDL-cholesterol levels. This study is considered meaningful for the innovation of secondary prevention strategies in patients with prior coronary artery disease. We measure the intima-media thickness of carotid arteries as a surrogate marker for evaluating the effects of probucol on the prevention of cerebro- and cardiovascular events. Because several recent studies have shown that high-sensitivity CRP (hs-CRP) is a strong and independent predictor of cardiovascular events independent of LDL-C levels or the existence of metabolic syndrome, we add a measurement of hs-CRP and adiponectin levels for assessing the mechanisms underlying the anti-atherogenic effects of probucol. Furthermore, in Western countries, probucol use has been discontinued because of the manufacturer's withdrawal notice to the Food and Drug Administration (FDA) of the United States in 1995. This was because probucol was believed to prolong the electrocardiographic QTc interval, resulting in lethal arrhythmias such as ventricular tachycardia. However, few Japanese studies...
of probucol showed the correlation between probucol treatment and the prolongation of the QTc interval. Probucol has been recommended as a treatment for the prevention of atherosclerotic cardiovascular diseases in the JAS Guidelines; however, the evidence from clinical trial was poor. In the current study, we will examine the safety of probucol for the prevention of secondary cardiovascular events.

**Study Design**

The PROSPECTIVE study is a randomized (1:1), prospective, open-label, multi-center clinical trial, and conducted on patients of hyper-LDL-cholesterolemia with a prior history of coronary events as coronary heart disease (CHD). This trial has been designed to evaluate the additional effect of probucol with other lipid-lowering drugs for the prevention of cerebro- and cardiovascular events. Thus, two arms of trial are a control group of patients on conventional lipid-lowering therapy (LLT) and a test group of patients on conventional LLT plus probucol treatment (Fig. 1). Our goal is to evaluate the additional effect of probucol combined with other lipid-lowering drugs for the prevention of cerebro- and cardiovascular events in patients with prior coronary events and high LDL-C levels. The protocol of the PROSPECTIVE study was initially reviewed and approved by the institutional review board (IRB) of Osaka University Hospital, and thereafter, the protocol was reviewed by the IRBs of the participating institutions. Investigators obtain IRB approval and permission from the head of each institution before conducting the study. This study is registered with UMIN (UMIN000003307, March 3, 2010).

**Study Population**

The trial enrolls men and women ≥20 years of age. As the key inclusion criteria, patients with all of the following 8 clinical statuses are enrolled (Fig. 1): 1) diagnosis of dyslipidemia with high LDL-C level (≥140 mg/dl) without any medication; 2) treatment using any lipid-lowering drugs including statins for ≥8 weeks before providing informed consent; 3) serum LDL-C level <200 mg/dl within 8 weeks before providing informed consent, as calculated by Friedewald’s formula (LDL-C = total cholesterol – HDL-cholesterol – triglycerides (TG)/5); 4) history of acute myocardial infarction or angina pectoris ≥3 months before providing informed consent, old myocardial infarction, coronary artery bypass grafting (CABG) ≥3 months earlier, PCI ≥9 months earlier, or PCI with no restenosis that was diagnosed by follow-up coronary angiography at 6–9 months after PCI; 5) normal cardiac function, mild or moderate heart failure (NYHA classification I or II); 6) ≥20 years of age at the time of informed consent; 7) no severe hepatic and renal dysfunction (AST <100 IU/L, ALT <100 IU/L, serum creatinine <1.5 mg/dl) within 4 weeks before providing informed consent; and 8) signed written informed consent for participation in this study. Exclusion criteria are the presence
of the following clinical statuses at the time of informed consent: 1) ongoing treatment with probucol within 6 months before the time of informed consent; 2) ongoing treatment with cyclosporine; 3) history of hypersensitivity reactions to probucol; 4) diagnosis of FH based on the NICE Clinical Guideline 71 [1]; 5) very high TG level (>400 mg/dl) within 8 weeks before providing informed consent; 6) markedly high HbA1c level (≥8%) on the most recent blood test; 7) frequent multifocal ventricular arrhythmia; 8) atrial fibrillation (Af) including paroxysmal Af; 9) long QTc interval on a resting electrocardiogram (>450 ms in males or >470 ms in females); 10) congestive heart failure (NYHA III or IV) or unstable angina; 11) participation in other clinical trials; 12) women who are pregnant, are lactating, may be pregnant or wish to be pregnant within the study period; or 13) inappropriate candidate for participation as assessed by the doctors in the current study.

Randomization and Treatment Protocol

During screening, patients are evaluated according to the inclusion and exclusion criteria. Institutions and patients are registered through a web-based central registration system provided by the data center of the study. Once the primary physician had obtained patient consent, access to the system was granted and the physician sent the information required for enrollment. The system automatically evaluated the eligibility of each patient and randomly assigned patients to either the control group (conventional LLT continued) or the test group (LLT with probucol) with 1:1 allocation rate. In randomization, LDL-C level (≥140 mg/dl vs. <140 mg/dl), diabetes (with vs. without), and hypertension (with vs. without) are dynamically balanced between the two groups as adjusted allocation factors (Fig. 1). As a protocol treatment, each of the lipid-lowering agents is administered continuously during the study period in control group and probucol (500 mg/day, 250 mg twice daily at morning and after dinner) is added to LLT in the test group within 6 weeks after the registration. All data are input to the case report after the protocol treatment is initiated. If serious adverse events (SAEs) are observed during the protocol treatment or within 30 days after protocol treatment, they are evaluated according to the predetermined reporting schedule and graded according to NCI-CTCAE. SAEs include the following adverse events: death, clinical events that could result in death, those that require hospital admission or extended hospitalization, disorders, clinical events that could result in disorders, others that are serious and the former adverse events, or congenital disease or abnormality in post-generations. SAEs are reported promptly; the efficacy and safety evaluation committee evaluates these and recommends and determines countermeasures. During the study period, the following parameters are determined before the protocol treatment and at 3 months, 1, 2, and 3 years after registration, during termination and the simultaneous outcome: patient’s background, maximum (max)/minimum (min) intima-media thickness (IMT), total cholesterol, TG, HDL-C, hs-CRP, adiponectin, all cerebro- and cardiovascular events, all adverse events and the confirmation of being alive.

End Points

We hypothesized that the addition of probucol to LLT will reduce the incidence of the primary end points (i.e., cerebro- or cardiovascular events; death because of cardiovascular diseases including sudden death, nonfatal myocardial infarction, nonfatal cerebral stroke excluding transient ischemic attack, hospitalization for unstable angina, hospitalization for heart failure or coronary revascularization such as PCI or CABG after at least 3 years of follow-up compared with LLT alone. The primary efficacy end point is the presence of and the time from registration until the first occurrence of cerebro- and cardiovascular events. Cerebro- and cardiovascular events are recognized as: 1) cardiovascular death including cardiac sudden death; 2) nonfatal myocardial infarction; 3) nonfatal cerebral stroke excluding transient ischemic attack (TIA); 4) hospital admission because of unstable angina, 5) hospital admission because of heart failure; and 6) all coronary revascularizations with either PCI or CABG. The secondary efficacy and safety end points are as follows: 1) all death; 2) all cerebro- and cardiovascular disease; 3) event-free survival time; 4) levels of the mean IMT of carotid arteries and their changes; 5) levels of max IMT in common or internal carotid arteries and their changes; and 6) severe adverse events and their frequency.

Statistical Design and Analysis

As shown in the randomized prospective study of primary prevention for common carotid atherosclerosis in Japan using probucol, the Fukuoka Atherosclerosis Trial (FAST) [13] (a randomized prospective study), the morbidity of cerebro- and cardiovascular events within 2 years of the observation period was 2.4% in the probucol-treated group, which was half that in the lipid-lowering agent-treated group (4.8%). Simultane-
ously, there are no secondary prevention studies in patients with dyslipidemia who had a prior history of cardiovascular events in Japan, except for the report evaluating the effect of probucol on secondary prevention in patients with FH. Therefore, when we referred to the result of the Japan EPA Lipid Intervention Study (JELIS) that compared the effect of eicosapentaenoic acid (EPA) in addition to statins with regard to the secondary prevention of cardiovascular events; the morbidity of cardiovascular events in patients treated with statins (pravastatin or simvastatin) for the secondary prevention of cardiovascular diseases was 10.7% for 5 years.

On considering the sample size in the study, we assumed that the morbidity of cerebro- and cardiovascular events in the control group would be 10.7% based on the results from the statin-treated group of the JELIS study. In the test group, we assumed that the rate would be 5.4%, approximately half of that in the statin-treated group because the addition of probucol to conventional LLT may improve the morbidity of cardiovascular events and the primary prevention shown in the FAST study. With regard to the condition, sample size per group was calculated as 408 patients with significance level by two-tailed as 0.05 and the power as 0.8 in a 4-year accrual period and 3-year follow-up. Considering that several patients will be dropped out from the analysis, we decided that the target number of patients in one group was 430 and total target number of patients in this study was 860.

The patient population in the statistical analysis was a full analysis set based on intention to treat principle. The characteristics of patients’ demographics and baseline values are compared between the two groups. For the primary efficacy end point, the presence and time from registration until the first cerebrovascular and cardiovascular events will be analyzed. By estimating event-free survival curves using the Kaplan–Meier method and the 95% confidence interval at 1, 2, and 3 years, event-free survival curves for the two groups are compared using the log-rank test stratified with random allocation factors: LDL-C level (≥140 mg/dl vs. <140 mg/dl), diabetes (with vs. without) and hypertension (with vs. without). The secondary endpoints of the period until all death, all cardio- and cerebrovascular disease, and event-free survival time will be analyzed in the same way as the primary end point. Levels of the mean- and max-IMT of carotid arteries from baseline to 1, 2, and 3 years will be analyzed by mixed-effects model with repeated measurements with group, visit, and baseline value as fixed effect and patient as random effect, comparing among groups will be performed. Frequency of SAEs will be summarized by preferred term and intensity and compared using Fisher’s exact test. The significant level in statistical analysis is 0.05 with two-tailed. All statistical analyses will be done with SAS version 9.3.

**Study Organization**

The executive committee is working on the study design, execution, protocol amendments, and the supervision of the study. It must adjust the various issues that may occur during the execution of the study and review the process of the study at appropriate time points to maintain the safety of patients and the integrity of the study. The project director manages the review of the protocol in the IRB of Osaka University Hospital, communicates the approved protocol to participating institutions, and addresses every unexpected complication that may occur during the execution of the study by adjusting for more appropriate progression. The advisory board provides advice regarding the appropriate management and the scientific significance of the study. The protocol committee creates the protocol, examines the requirement for the protocol revision if the probability for protocol revision appears during the execution of the study, and reports it to the principal investigator. The study data center is independent of all committees and is planning to maintain and review all study data. The efficacy and safety evaluation committee evaluates the following reports to recommend early termination or study changes to the principal investigator: 1) the report of severe adverse events that is sent from the principal investigator at appropriate time points; 2) related reports from other studies such as papers and conference presentations at an appropriate time point; 3) the report of study progress from the data center every 3 months during the registration period or every 6 months after registration; and 4) total results of the safety information. The cerebro- and cardiovascular events evaluation committee determines whether the reported issue corresponds to the cerebro- and cardiovascular event recognized as a primary end point in this study unless it appears to be clearly relevant.

**Current Status**

Acceptance of the protocol by the IRB of Osaka University Hospital occurred on June 29, 2010, and the recruitment of the patients initiated thereafter. A total of 874 patients have been enrolled up to the end of the recruitment on February 28, 2014, and the study will be terminated on February 28, 2017 after
evaluating the simultaneous outcome.

**Context**

Several randomized controlled trials have indicated that lowering the levels of total cholesterol and LDL-C is effective for the prevention of atherosclerotic cardiovascular diseases (ASCVDs). However, cholesterol-lowering agents cannot completely prevent the ASCVD events even in patients who achieve low LDL-C values. Probucol decreases serum LDL-C concentration by enhancing the excretion of cholesterol into the bile, inhibits the oxidative modification of LDL and attenuates the free-radical peroxidation of lipids. These characteristics of probucol may result in an anti-atherogenic lipid and lipoprotein profile in patients with ASCVD.

Although several epidemiological studies have shown that high HDL-C levels are correlated with low morbidity of CHD events, plasma cholesteryl ester transfer protein (CETP) inhibitors that increase HDL-C levels did not prevent CHD events or the progression of carotid atherosclerosis; other studies have shown that they actually increased the morbidity of CHD events. Epidemiological studies showed that plasma CETP activity/mass had negative correlations with CHD events. Probucol decreases serum HDL-C by 30% by activating CETP, which increases small cholesteryl ester-poor HDL and prebeta HDL with a strong capacity for cholesterol efflux and activates reverse cholesterol transport (RCT). Therefore, probucol-mediated enhancement of CETP activity may be a novel strategy for the prevention and regression of atherosclerosis. Probucol ameliorates atherosclerotic status by suppressing macrophage infiltration and MMP expression in atherosclerotic plaques in an animal model of hypercholesterolemia (WHHL rabbits). Probucol enhances various anti-atherosclerotic functions of HDL such as antioxidative, anti-inflammatory, and antithrombotic effects. Moreover, probucol prevents lipid storage by suppressing the uptake and stimulating the release of cholesterol from macrophages and is effective for the regression of xanthelasma and Achilles tendon xanthomas in patients with FH.

Recent study has been demonstrated that probucol decreased coronary plaque in combination with cilostazol (SECURE study). These clinical and experimental data strongly suggest the efficacy of probucol for preventing secondary cardiovascular events.

Because probucol use has been discontinued in USA, the efficacy of probucol for preventing ASCVD has been investigated mainly in Asian countries, including Japan. In the Probucol Quantitative Regression Swedish Trial (PQRST), probucol did not decrease the lumen volume of femoral arteries in hypercholesterolemic patients. However, it reduced the restenosis rate after percutaneous transluminal angioplasty in patients with intermittent claudication. In FAST as described above, probucol and pravastatin significantly reduced IMT and the incidence of cardiac events compared with placebo treatment in asymptomatic hypercholesterolemic patients. Probucol markedly improved long-term survival by decreasing all-cause death and the incidence of cardiac events as well as clinical events. Our previous epidemiological study, “Probucol Observational Study Illuminating Therapeutic Impact on Vascular Events (POSITIVE),” revealed that long-term treatment with probucol was associated with reduced risk of secondary cardiovascular events in a very-high-risk population such as patients with heterozygous FH. Multi-variate Cox regression analysis estimated the hazard ratio (HR) of probucol use was 0.13 in patients for secondary prevention. Recent study has been demonstrated that probucol prolonged the electrocardiographic QTc interval, which may result in lethal ventricular arrhythmias. However, no fatal ventricular arrhythmias have been reported in other studies, including the POSITIVE study. Recently, in the Canadian Antioxidant Restenosis Trial (CART-1), safety and efficacy were compared between probucol and a probucol analog, succinobucol. Both succinobucol and probucol reduced restenosis after PCI and prolongation of the QTc interval was more frequent in the probucol group than in the succinobucol group. However, in other studies of probucol, the
correlation between probucol treatment and prolongation of the QTc interval has not been proven; probucol had a low frequency of adverse events. In the PROSPECTIVE study, we will examine the safety and efficacy of probucol for the prevention of secondary cardiovascular events in a prospective study.

Our PROSPECTIVE study may reveal, for the first time, the efficacy and safety of the use of probucol in addition to statins or other lipid-lowering therapy for reducing major atherosclerotic cardiovascular events in patients with hypercholesterolemia and prior coronary events.

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COI Disclosures

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Appendix

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