Study Profile

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

Shizuya Yamashita1, 2, Daisaku Masuda3, Tohru Ohama3, 4, Hidenori Arai5, Hideaki Bujo6, Tatsuo Kagimura7, Toru Kita8, Masunori Matsuzaki9, Yasushi Saito10, Masanori Fukushima7 and Yuji Matsuzawa11 on behalf of the PROSPECTIVE Study Group

1Department of Community Medicine, Osaka University Graduate School of Medicine, Suita, Osaka, Japan
2Rinku General Medical Center, Izumisano, Osaka, Japan
3Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Osaka, Japan
4Department of Dental Anesthesiology, Osaka University Graduate School of Dentistry, Suita, Osaka, Japan
5The National Center for Geriatrics and Gerontology, Obu, Aichi, Japan
6Department of Clinical Laboratory and Experimental Research Medicine, Toho University, Sakura Medical Center, Sakura, Chiba, Japan
7Foundation for Biomedical Research and Innovation, Kobe, Hyogo, Japan
8Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan
9Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi, Japan
10Chiba University Graduate School of Medicine, Chiba, Japan
11Sumitomo Hospital, Osaka, Japan

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.

J Atheroscler Thromb, 2016; 23: 746-756.

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-
Atherosclerosis Society (JAS) Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases (revised in 2012)\textsuperscript{1)}, the primary prevention of cerebro- and cardiovascular disease in patients with dyslipidemia was defined as follows: the first step for prevention is lifestyle modification; however, if the modification does not help to achieve the target lipid profile goal, drug intervention will be considered according to the weight of the individual risk factors. Statins are the most frequently used drugs to treat dyslipidemia worldwide. Statins decrease serum low-density lipoprotein (LDL) cholesterol (LDL-C) levels by inhibiting the hepatic synthesis of cholesterol via inhibition of HMG CoA-reductase, decreasing intrahepatic cholesterol pool, and enhancing the LDL uptake through LDL receptor. It has been strongly suggested that statins prevent the onset and recurrence of cardiovascular diseases. Clinical trials such as 4S\textsuperscript{2)}, CARE\textsuperscript{3)}, and LIPID\textsuperscript{4)} indicated that statins decreased the risk of cardiovascular events by approximately 30%. A meta-analysis including intensive statin therapy showed a significant reduction in the odds ratio of coronary death or myocardial infarction (\(-16\%, P=0.00003\) \textsuperscript{5}). However, although intensive statin therapy showed significant efficacy in reducing cardiovascular risks, atherosclerotic events have not been completely prevented, and “residual risks” remain. Therefore, new and effective pharmacologic therapies should be used in combination with statins.

Since Barnhart et al. reported in the 1970s that probucol had a cholesterol-lowering effect\textsuperscript{6)}, it has been used as a drug for hypercholesterolemia. Since 1985, probucol has been used in Japan in >60,000 patients with hyperlipidemia. Probucol reduces serum cholesterol levels by enhancing the catabolic rate of LDL, excreting cholesterol into the bile and inhibiting the early steps of cholesterol synthesis\textsuperscript{7, 8)}. Probucol has a potent antioxidative effect and inhibits the oxidation of LDL, which is different from the action of statins as anti-hypercholesterolemic drugs\textsuperscript{9)}. Statins inhibit the transportation of cholesterol from the liver to peripheral cells, whereas probucol enhances reverse cholesterol transport from atheromatous plaques to the liver\textsuperscript{10, 11)}, resulting in the significant regression of xanthelasmas and Achilles tendon xanthomas in patients with familial hypercholesterolemia (FH)\textsuperscript{12)}. 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\textsuperscript{13)}, reduced restenosis and the revascularization rate after percutaneous coronary intervention (PCI)\textsuperscript{14, 15)}, and improved endothelium-dependent coronary vasomotion\textsuperscript{16)} and common carotid atherosclerosis in patients with hypercholesterolemia\textsuperscript{17)}. 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\textsuperscript{18}). 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\textsuperscript{19)} 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\cite{20}. 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 or angina pectoris >3 months before providing informed consent, 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 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\cite{20}. 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 or angina pectoris >3 months before providing informed consent, 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 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\cite{20}. 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 or angina pectoris >3 months before providing informed consent, 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 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\cite{20}. 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 or angina pectoris >3 months before providing informed consent, 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 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\cite{20}. In the current study, we will examine the safety of probucol for the prevention of secondary cardiovascular events.
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\textsuperscript{21}; 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 cerebrovascular 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 follows: 1) cardiovascular death including cardiac sudden death; 2) nonfatal myocardial infarction; 3) nonfatal cerebrovascular 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)\textsuperscript{15} (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 cerebro- 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 (~10%–20%) 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 pre-beta 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 anti-thrombotic 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. 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 (~13.9%) and the incidence of cardiac events (2.4%) compared with placebo treatment (23.2% and 13.6%, and 0.055, respectively) in asymptomatic hypercholesterolemic patients. Probucol markedly improved long-term survival by decreasing all-cause death (HR, 0.65; p=0.036 [conventional adjustment model] and HR, 0.57; p=0.008 [propensity score adjusted model], respectively) following complete revascularization in patients with CHD assessed by a propensity score. Moreover, the administration of probucol prevented restenosis after PCI in a small trial of Japanese patients, and the restenosis rate and repeat angioplasty in patients who received probucol 30 days prior to angioplasty up to 6 months (Multivitamins and Probucol Study, MVP). In the Probucol Angioplasty Restenosis Trial (PART), probucol, which was administered 4 weeks prior to angioplasty and continued for 6 months, significantly reduced the rate of restenosis as well as clinical events (17% vs. 36%, p=0.04). 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 (95% CI 0.05–0.34, p<0.001) in patients for secondary prevention. Recent study has been demonstrated that probucol decreased coronary plaque in combination with cilostazol (SECURE study). These clinical studies clearly showed that probucol may be effective for the prevention of coronary restenosis and secondary cardiovascular events in patients with hypercholesterolemia and prior cardiovascular events.

In Western countries, the use of probucol was discontinued because 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.

Acknowledgments

The authors thank the patients and their families and appreciate the study participants, physicians, supporting medical staff, and co-workers for their assistance in the preparation and execution of this study. We thank Kaori Hizu-Shioyama, Risa Wada, Ayami Saga, and Kyoko Ozawa for their excellent administrative and technical assistance. The authors thank the following additional investigators for their contributions to this trial: Koichi Yamashiro and Shinsuke Kojima for project management; Kenichi Kono and Takashi Yamauchi for data management; and Yoshihiro Matsubara for statistical analyses.

COI Disclosures

This study was conducted in collaboration between Osaka University and the Foundation for Biomedical Research and Innovation. The latter organization receives unconditional research grants from several pharmaceutical companies (AstraZeneca K.K., Dai-ichi Sankyo Co., Ltd., Astellas Pharma Inc., Novartis Pharma K.K., Chugai Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., Sanofi K.K.). However, these companies were not involved in the design and execution of this study. Additionally, no company provided probucol for this study and has reviewed the current manuscript. SY has received consulting and/or lecture fees from MSD KK, Bayer Yakuhin, Ltd, Kowa Pharmaceutical Co., Ltd., Sanwa Kagaku Kenkyusho Co., Ltd., Shionogi & Co., Ltd., Medical Review Co., Ltd., and Skylight Biotech, Inc. SY has received research funding from Sanwa Kagaku Kenkyusho Co., Ltd., Kowa Pharmaceutical Co., Ltd., Kyowa Medex Co., Ltd., Nippon Boehringer Ingelheim Co., Ltd., Ono Pharmaceutical Co., Ltd. and Mochida Pharmaceutical Co., Ltd. HA has received consulting and/or lecture fees from Dai-ichi Sankyo Co., Ltd., MSD KK, Kowa, and research funding from Dai-ichi Sankyo Co., Ltd. and Otsuka Pharmaceutical Co., Ltd. YS has received lecture fees from Takeda Pharmaceutical Co. Ltd. YM has received advisory fees from Teijin Pharma Co. and Otsuka Pharmaceutical Co. DM, TO, HB, TK, MM and MF have nothing to disclose.

Appendix

Executive Committee:

Principal Investigator: Shizuya Yamashita. Professor, Department of Community Medicine, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

Vice Principal Investigator: Hidenori Arai. Deputy Director, The National Center for Geriatrics and Gerontology, Obu, Aichi, Japan.

Hideaki Bujo. Department of Clinical-Laboratory and Experimental-Research Medicine, Toho University, Sakura Medical Center, Sakura, Chiba, Japan

Project Director: Daisaku Masuda. Assistant Professor, Department of Cardiovascular Medicine, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

Project Manager: Tohrui Ohama, Assistant Professor, Department of Dental Anesthesiology, Osaka University Graduate School of Dentistry, Suita, Osaka, Japan

Advisory Board:

Yuji Matsuzawa. President, Sumitomo Hospital, Osaka, Japan

Toru Kita. President, Kobe City Medical Center General Hospital, Kobe, Hyogo, Japan

Yasushi Saito. Professor Emeritus, Graduate School of Medicine, Chiba University, Chiba, Japan

Masunori Matsuzaki. Professor Emeritus, Yamanouchi University Graduate School of Medicine, Ube, Yamaguchi, Japan

Protocol Committee:

Hiroshi Nagai. President, Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kobe, Hyogo, Japan

Mariko Harada-Shiba. Director, Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Suita, Osaka, Japan

Tohrui Ohama, Assistant Professor, Department of Dental Anesthesiology, Osaka University Graduate School of Dentistry, Suita, Osaka, Japan
Imaging Evaluation Committee:
Hiroyuki Daida. Professor, Department of Cardiology, Juntendo University School of Medicine, Tokyo, Japan
Masao Moroi. Associate Professor, Department of Cardiology, Toho University Ohashi Medical Center, Tokyo, Japan
Hiroshi Matsuo. President, Matsuo Clinic, Yao, Osaka, Japan
Toshimasa Fujiwara, Medical Director, Chibaken Saiseikai Narashino Hospital, Narashino, Nagano, Japan

Trial Statistician: Tatsuo Kagimura. Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kobe, Hyogo, Japan

Data Center: Translational Research Informatics Center, Foundation for Biomedical Research and Innovation, Kobe, Hyogo, Japan

Efficacy and Safety Evaluation Committee:
Chairperson: Jun Sasaki. Professor, Graduate School of Health and Welfare Sciences, International University of Health and Welfare Graduate School, Ohtawara, Fukuoka, Japan
Seiji Umemoto. Deputy Director, Center For Clinical Research, Yamaguchi University Hospital, Ube, Yamaguchi, Japan
Shigeyuki Matsui. Professor, Department of Data Sciences, The Institute of Statistical Mathematics, Tachikawa, Tokyo, Japan
Hidenao Fukuyama. Professor, Human Brain Research Center, Graduate School of Medicine Kyoto University, Kyoto, Japan

Cerebro- and Cardiovascular Events Evaluation Committee:
Takeshi Kimura. Professor, Department of Cardiovascular Medicine, Graduate School of Medicine, Kyoto University, Kyoto, Japan
Akira Sumitsuji. Associate Professor, Department of Advanced Cardiovascular Therapeutics, Osaka University Graduate School of Medicine, Saita, Osaka, Japan
Kazuo Kitagawa. Professor, Department of Neurology, Graduate School of Medicine, Tokyo Women’s Medical University, Tokyo, Japan

References
1) Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hirobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokode M, Yokote K; Japan Atherosclerosis Society. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. J Atheroscler Thromb. 2013; 20: 517-523
2) Scandinavian Simvastatin Survival Study Group: Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). The Lancet. 1994; 344: 1383-1389
3) Plehn J F, Davis B R, Sacks F M, Rouleau JL, Pfeffer MA, Bernstein V, Cuddy TE, Moyé LA, Piller LB, Rutherford J, Simpson LM, Braunwald E: Reduction of Stroke Incidence After Myocardial Infarction With Pravastatin The cholesterol and recurrent events (CARE) study Circulation. 1999; 99: 216-223
4) The Long-Term Intervention with Pravastatin in Isch-aemic Disease (LIPID) Study Group: Prevention of Cardiovascular events and death with Pravastatin in patient with Coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998; 339: 1349-1357
5) 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: 438-445
6) Barnhart JW, Sefranka JA and McIntosh DD: Hypocholesterolemic effect of 4,4’-(isopropylidenedithio)-bis(2,6-di-t-butylpheol) (Probucol). Am J Clin Nutr. 1970; 23: 1229-1233
7) Tomikawa M, Nakayasu T, Tawara K and Abiko Y: Effect of Probucol on serum lipoprotein levels in normal and dyslipoproteinemic mice. Atherosclerosis. 1981; 40: 101-113
8) Yamashita S, Matsuzawa Y. Where are we with probucol: a new life for an old drug? Atherosclerosis. 2009; 207: 16-23
9) Kita T, Nagano Y, Yokode M, Ishik K, Kume N, Ooshima A, Yoshida H, Kawai C: Probucol prevents the progression of atherosclerosis in Watanabe heritable hyperlipidemic rabbit, an animal model for familial hypercholesterolemia. Proc Natl Acad Sci USA. 1987; 84: 5928-5931
10) Ishigami M, Yamashita S, Sakai N, Hirano K, Maruyama T, Takami S, Koyama M, Kameda-Takemura K, Matsuzawa Y. High-density lipoproteins from probucol-treated patients have increased capacity to promote cholesterol efflux from mouse peritoneal macrophages loaded with acetylated low-density lipoproteins.Eur J Clin Invest. 1997; 27: 285-292
11) Rinninger F, Wang N, Ramakrishnan R, Jiang XC, Tall AR: Probucol enhances selective uptake of HDL-associated cholesteryl esters in vitro by a scavenger receptor B-I-dependent mechanism.Arterioscler Thromb Vasc Biol. 1999; 19: 1325-1332
12) Matsuzawa Y, Yamashita S, Funahashi T, Yamamoto A and Tarui S: Selective reduction of cholesterol in HDL2 fraction by probucol in familial hypercholesterolemia and hyper HDL2 cholesteroloma with abnormal cholesteryl ester transfer. Am J Cardiol. 1988; 62: 668-72B
13) Shinomiya M, Nishide T, Tashiro J, Shirai K, Saito Y,
Yoshida S: Effect of 5-Year administration of probucol on development of myocardial infarction in heterozygous familial hypercholesterolemia. Curr Therapeut Res. 1993; 54: 142-151

14) Daida H, Kuwabara Y, Yokoi H, Nishikawa H, Takatsu F, Nakata Y, Kutsumi Y, Oshima S, Nishiyama S, Ishiwata S, Kato K, Nishimura S, Miyachi K, Kanoh T, Yamaguchi H: Effect of probucol on repeat revascularization rate after percutaneous transluminal coronary angioplasty (from the Probucol Angioplasty Restenosis Trial [PART]). Am J Cardiol. 2000; 86: 550-552

15) Tardif J-C, Cote G, Lesperance J, Bourassa M, Lambert J, Doucet S, Bilodeau L, Nattel S, de Guise P: Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. N Engl J Med. 1997; 337: 365-372

16) Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, Anderson TJ, Meredith IT, Yeung AC, Frei B, Selwyn AP, Ganz P: The effect of cholesterol-lowering and antioxidant therapy on endothelium-dependent coronary vaso-motion. N Engl J Med. 1995; 332: 488-493

17) Sawayama Y, Shimizu C, Maeda N, Tatsukawa M, Kinukawa N, Koyanagi S, Kashihashi S, Hayashi J: Effects of Probucol and Pravastatin on Common Carotid Atherosclerosis in Patients with Asymptomatic Hypercholesterolemia. Fukuoka Atherosclerosis Trial (FAST). J Am Coll Cardiol. 2002; 39: 610-616

18) Yamashita S, Buo H, Arai H, Harada-Shiba M, Matsu S, Fukushima M, Saito Y, Kita T, MatsuZawa Y: Long-Term probucol treatment prevents secondary cardiovascular events: a cohort study of patients with heterozygous familial hypercholesterolemia in Japan. J Atheroscler Thromb. 2008; 15: 292-303

19) Ridker PM, Danielsen E, Fonseca FA, Genest J, Goto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, Nordestgaard BG, Shepherd J, Willerson JT, Glynn RJ: JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008; 359: 2195-2207

20) Teramoto T, Sasaki J, Ishishashi S, Birou S, Daida H, Dohi S, Egusa G, Hiro T, Hikobe K, Iida M, Kihara S, Kinoshita M, Maruyama C, Ohta T, Okamura T, Yamashita S, Yokokura H, Yomura K: Treatment B) drug therapy: executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan-2012 version. J Atheroscler Thromb. 2013; 20: 850-860

21) Marks D, Thorogood M, Neil HA, Humphries SE: A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. Atherosclerosis. 2003; 168: 1-14

22) Yokoyama M, Ogisaka H, MatsuMaki M, MatsuZawa Y, Saito Y, Ishikawa T, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K: Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007; 369: 1090-1098

23) Cholesterol Treatment Trialists’ (CTT) Collaborators, Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, Voysey M, Gray A, Collins R, Baigent C. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomized trials: prospective meta-analysis of data. Lancet 2012; 380: 581-590

24) Cholesterol Treatment Trialists’ (CTT) Collaboration, Fulcher J, O’Connell R, Vossey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, Braunwald E, La Rosa J, Pedersen TR, Tonkin A, Davis B, Sleigh P, Franzosi MG, Baigent C, Keech A: Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174 000 participants in 27 randomised trials. Lancet 2015; 385: 1397-1405

25) Expert Dyslipidemia Panel of the International Atherosclerosis Society Panel members. An International Atherosclerosis Society Position Paper: global recommendations for the management of dyslipidemia -- full report. J Clin Lipidol 2014; 8: 29-60

26) Stone NJ, Robinson JG, Lichtenstein AH, Barrey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr, Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bosskurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr, Tomaselli GF; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 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. Circulation 2014; 129(Suppl 2): S1-45

27) The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias. Eur Heart J 2011; 32 (14): 1769-1818

28) Superko HR, King S, 3rd. Lipid management to reduce cardiovascular risk: a new strategy is required. Circulation 2008; 117: 560-568

29) Buckley MM, Goo KL, Price AH, Brodgen RN: Probucol. A reappraisal of its pharmacological properties and therapeutic use in hypercholesterolaemia. Drugs 1989; 37: 761-800

30) Tawara K, Tomikawa M, Abiko Y. Mode of action of probucol in reducing serum cholesterol in mice. Jpn J Pharmacol 1986; 40: 123-133

31) Cristol LS, Jialal I, Grundy SM. Effect of low-dose probucol therapy on LDL oxidation and the plasma lipoprotein profile in male volunteers. Atherosclerosis 1992; 97: 11-20

32) Kaminsky AI, Lankin VZ, Perepelitsa EI, Konovalova
GG, Samko AN, Tikhaze AK, Kukharchuk VV, Belenkov YN: Relationship between free-radical lipid oxidation and efficiency of coronary angioplasty in coronary patients. Bull Exp Biol Med 2007; 144: 664-666

33) Carew TE, Schwenke DC, Steinberg D. Antiatherogenic effect of probucol unrelated to its hypocholesterolemic effect: evidence that antioxidants in vivo can selectively inhibit low density lipoprotein degradation in macrophage-rich fatty streaks and slow the progression of atherosclerosis in the Watanabe heritable hyperlipidemic rabbit. Proc Natl Acad Sci USA 1987; 84: 7725-7729

34) Kita T, Yokode M, Ishii K, Kume N, Nagano Y, Arai H, Otani H, Ueda Y, Haru S: The role of oxidized lipoproteins in the pathogenesis of atherosclerosis. Clin Exp Pharmacol Physiol Suppl 1992; 20: 37-42

35) Barter PJ, Caufield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M, Lopez-Sendon J, Mosca L, Tardif JC, Wåters DD, Shear CL, Revkin JH, Buhr KA, Fisher MR, Tall AR, Brewer B; ILLUMINATE Investigators: Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med 2007; 357: 2109-2122

36) Kastelein JJ, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ, Revkin JH, Grobbee DE, Riley WA, Shear CL, Duggan WT, Bots ML; RADIANCE 1 Investigators: Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. N Engl J Med 2007; 356: 1620-1630

37) Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brummt J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS; dal-OUTCOMES Investigators: Effects of dalceptrapib in patients with a recent acute coronary syndrome. N Engl J Med 2012; 367: 2089-2099

38) Zhong S, Sharp DS, Grove JS, Bruce C, Yano K, Curb JD, Tall AR: Increased coronary heart disease in Japanese-American men with mutation in the cholesteryl ester transfer protein gene despite increased HDL levels. J Clin Invest 1996; 97: 2917-2923

39) Hirano K, Yamashita S, Nakajima N, Arai T, Maruyama T, Yoshida Y, Ishigami M, Sakai N, Kameda-Takemura K, Matsuzawa Y: Genetic cholesteryl ester transfer protein deficiency is extremely frequent in the Omagari area of Japan. Marked hyperalphalipoproteinemia caused by deficiency is extremely frequent in the Omagari area of Japan. Clin Invest 1996; 97: 2917-2923

40) McPherson R, Hogue M, Milne RW, Tall AR, Marcel YL: Increase in plasma cholesterol ester transfer protein during probucol treatment. Relation to changes in high density lipoprotein composition. Arterioscler Thromb 1991; 11: 476-481

41) Chiesa G, Michelagnoli S, Cassinotti M, Gianfranceschi G, Werba JP, Pazzucconi F, Sirtori CR, Franceschini G: Mechanisms of high-density lipoprotein reduction after probucol treatment: changes in plasma cholesterol esterification/transfer and lipase activities. Metabolism 1993; 42: 229-235

42) Ishigami M, Yamashita S, Sakai N, Hirano K, Arai T, Maruyama T, Takami S, Koyama M, Kameda-Takemura K, Matsuzawa Y: High-density lipoproteins from probucol-treated patients have increased capacity to promote cholesterol efflux from mouse peritoneal macrophages loaded with acetylated low-density lipoproteins. Eur J Clin Invest 1997; 27: 285-292

43) Adlouni A, El Messal M, Saile R, Parra H, Fruchart J, Ghalim N: Probucol promotes reverse cholesterol transport in heterozygous familial hypercholesterolemia. Effects on apolipoprotein AI-containing lipoprotein particles. Atherosclerosis 2000; 152: 433-440

44) Li S, Liang J, Niimi M, Bilal Waqar A, Kang D, Koike T, Wang Y, Shiomi M, Fan J. Probucol suppresses macrophage infiltration and MMP expression in atherosclerotic plaques of WHHL rabbits. J Atheroscler Thromb 2014; 21: 648-658

45) Smith JD. Dysfunctional HDL as a diagnostic and therapeutic target. Arterioscler Thromb Vasc Biol 2010; 30: 151-155

46) Inagaki M, Nakagawa-Toyama Y, Nishida M, Nakatani K, Nakaoka H, Kawase M, Kawase R, Tsubakio-Yamamoto K, Matsuda D, Ohama T, Matsuyama A, Ishigami M, Komuro I, Yamashita S: Effect of probucol on antioxidant properties of HDL in patients with heterozygous familial hypercholesterolemia. J Atheroscler Thromb 2012; 19: 643-656

47) Yamamoto A, Hara H, Takaichi S, Wakisugi J, Tomikawa M: Effect of probucol on macrophages, leading to regression of xanthomas and atheromatous vascular lesions. Am J Cardiol 1988; 62: 31B-36B

48) Yamamoto A, Matsuzawa Y, Yokoyama S, Funahashi T, Yamamura T, Kishino B: Effects of probucol on xanthoma regression in familial hypercholesterolemia. Am J Cardiol 1986; 57: 643-656

49) Fujita M, Shirai K. A comparative study of the therapeutic effect of probucol and pravastatin on xanthelasmas. J Dermatol 1996; 23: 598-602

50) Blohdius G, Eriksson U, Olsson AG, Bergstrand L, Hådell K, Johansson J, Kaijser L, Lassvik C, Mölgaard J, Nilsson B: The effect of probucol on female atherosclerosis: the Probucol Quantitative Regression Swedish Trial (PQRST). Am J Cardiol 1994; 74: 875-883

51) Gallino Am Do DD, Alerci M, Baumgartner I, Cozzi L, Segatto M, Bernier J, Tutta P, Kellner F, Triller J, Schneider E, Amann-Vesti B, Studer G, Jager K, Aschwanden C, Canevascini E, Jacob AL, Kann R, Greiner R, Mahler F: Effects of probucol versus aspirin and versus brachytherapy on restenosis after femoropopliteal angioplasty:...
55) Kasai T, Miyauchi K, Kubota N, Kajimoto K, Amano A, Daida H: Probucol therapy improves long-term (>10-year) survival after complete revascularization: a propensity analysis. Atherosclerosis 2012; 220: 463-469
56) Setsuda M, Inden M, Hiraoka N, Okamoto S, Tanaka H, Okinaka T, Nishimura Y, Okano H, Kouji T, Konishi T: Probucol therapy in the prevention of restenosis after successful percutaneous transluminal coronary angioplasty. Clin Ther 1993; 15: 374-382
57) Tardif JC, Cote G, Lesperance J, Bourassa M, Lambert J, Doucet S, Bilodeau L, Nattel S, de Guise P: Probucol and multivitamins in the prevention of restenosis after coronary angioplasty. Multivitamins and Probucol Study Group. N Engl J Med 1997; 337: 365-372
58) Côté G, Tardif JC, Lespérance J, Lambert J, Bourassa M, Bonan R, Gosselin G, Joyal M, Tanguay JF, Nattel S, Gallo R, Crépeau J: Effects of probucol on vascular remodeling after coronary angioplasty. Multivitamins and Protocol Study Group. Circulation 1999; 99: 30-35
59) Yokoi H, Daida H, Kuwabara Y, Nishikawa H, Takatsu F, Tomihara H, Nakata Y, Kutsumi Y, Ohshima S, Nishiyama S, Seki A, Kato K, Nishimura S, Kano H, Yamaguchi H: Effectiveness of an antioxidant in preventing restenosis after percutaneous transluminal coronary angioplasty: the Probucol Angioplasty Restenosis Trial. J Am Coll Cardiol 1997; 30: 855-862
60) Daida H, Kuwabara Y, Yokoi H, Nishikawa H, Takatsu F, Nakata Y, Kutsumi Y, Oshima S, Nishiyama S, Ishiwata S, Kato K, Nishimura S, Miyauchi K, Kano H, Yamaguchi H: Effect of probucol on repeat revascularization rate after percutaneous transluminal coronary angioplasty (from the Probucol Angioplasty Restenosis Trial [PART]). Am J Cardiol 2000; 86: 550-552
61) Ko YG, Choi SH, Chol Kang W, Kwon Lee B, Wook Kim S, Shim WH. Effects of combination therapy with cilostazol and probucol versus monotherapy with cilostazol on coronary plaque, lipid and biomarkers: SECURE study, a double-blind randomized controlled clinical trial. J Atheroscler Thromb 2014; 21: 816-830
62) Tardif JC, Gregoire J, Schwartz L, Title L, Laramée L, Reeves F, Lespérance J, Bourassa MG, L’Allier PL, Glass M, Lambert J, Guertin MC; Canadian Antioxidant Restenosis Trial (CART-1) Investigators Effects of AGI-1067 and probucol after percutaneous coronary interventions. Circulation 2003; 107: 552-558