Study Design of SEASON Registry

Prospective Surveillance of Cardiovascular Events in Antiplatelet-Treated Arteriosclerosis Obliterans Patients in Japan (SEASON)

Yukihito HIGASHI,¹ MD, Masatoshi FUJITA,² MD, Hideki ORIGASA,³ PhD, Tetsuro MIYATA,⁴ MD, Hiroshi MATSUO,⁵ MD, Hiroaki NARITOMI,⁶ MD, and Hiroshi SHIGEMATSU,⁷ MD
on behalf of the SEASON investigators

SUMMARY

Antiplatelet therapy is widely performed for arteriosclerosis obliterans (ASO) to relieve ischemic symptoms and prevent cardiovascular events. However, the overall rate of cardiovascular events in patients with ASO under treatment with antiplatelet agents has not been fully investigated in Japan. The SEASON registry is a nationwide observational prospective cohort study designed to compile data from over 2,000 institutions across Japan, whose aims are to (1) understand the current status for the management of ASO and clarify the incidence of cardiovascular events in patients with ASO undergoing antiplatelet therapy, and (2) compare the effectiveness of sarogrelate, a 5-HT_{2A} receptor antagonist, in decreasing the event rate with those of other antiplatelet agents [UMIN ID: UMIN000003385]. The registry will recruit approximately 10,000 patients receiving antiplatelet therapy (8,000 patients for sarogrelate and 2,000 for other antiplatelet agents), and the patients will be followed every 6 months during a two-year follow-up period. The investigators plan to report all cardiovascular events and exacerbations of ASO. Analysis focusing on the sarogrelate-treated subgroup will also be performed. Exploratory analysis will be performed to determine the clinical characteristics of the patients and to elucidate the relationships between risk factors and cardiovascular events. The SEASON registry is the first attempt to create a nationwide database regarding the incidence of cardiovascular events in 10,000 ASO patients in Japan. In addition, it ultimately may enable us to conclude that sarogrelate prevents cardiovascular events. Information on the severity and risk factors in ASO patients in the clinical settings will be applicable to epidemiological analysis. (Int Heart J 2010; 51: 337-342)

Key words: Cohort study, Arteriosclerosis obliterans, Cardiovascular events, Prognosis, Antiplatelet therapy, Sarogrelate

Increasing attention has been paid to the prognosis of patients with peripheral arterial disease (PAD). In fact, population-based cohort studies^{1,2)} and retrospective studies on the outcome of PAD^{3,4)} have been conducted outside of Japan. Recent surveys of populations of patients with cardiovascular disease⁵⁾ or stroke⁶⁾ in Japan have produced significant interest in the impacts of low ankle-brachial pressure index (ABPI) and symptoms of intermittent claudication on prognosis. However, systematic epidemiological approaches to clarify this have been lacking.

The REDuction of Atherothrombosis for Continued Health (REACH) Registry has recently yielded the striking finding that patients with PAD have a higher risk of cardiovascular events than those with cardiovascular disease.^{7,8)} Cacoub, *et al*⁹⁾ showed in their one-year analysis of the REACH cohort that improved risk factor control was associated with a positive impact on cardiovascular event rates in PAD patients. They also found that risk factor control in PAD patients in Japan

achieved more favorable results than those in Western Europe and the Middle East, but considerably worse than those in North America.

The term arteriosclerosis obliterans (ASO) was formerly distinguished from PAD, since the latter includes thromboangiitis obliterans (TAO, Buerger's disease), which previously accounted for the majority of cases of peripheral arterial occlusive disease in Japan. With the dramatic decrease in the number of patients with TAO in recent decades, PAD has recently been used with almost the same meaning as ASO in Japan.¹⁰⁾ In Japan, coldness and numbness of the lower extremities caused by occlusion of lower limb arteries are considered to be early symptoms of ASO (Fontaine stage I), and antiplatelet therapy is performed even in the absence of the symptoms of intermittent claudication.

Oral antiplatelet therapy for ASO is widely performed in Japan, and several types of antiplatelet agents are currently available, including ticlopidine, prostaglandin I₂, prostaglandin

From the ¹ Department of Cardiovascular Physiology and Medicine, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, ² Human Health Sciences, Kyoto University Graduate School of Medicine, Kyoto, ³ Division of Biostatistics and Clinical Epidemiology, University of Toyama School of Medicine, Toyama, ⁴ Division of Vascular Surgery, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, ⁵ Matsuo Vascular Ultrasound Laboratory, Matsuo Clinic, Osaka, ⁶ Senrichuo Hospital, Osaka, and ⁷ Division of Vascular Surgery, Department of Surgery II, Tokyo Medical University, Tokyo, Japan.

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Address for correspondence: Yukihito Higashi, MD, Department of Cardiovascular Physiology and Medicine, Graduate School of Biomedical Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima, Hiroshima 734-8551, Japan.

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E1, cilostazol, eicosapentaenoic acid, and sarpogrelate. The three primary aims of antiplatelet therapy as described in “Guidelines for management of peripheral arterial occlusive diseases” released in 2009 by the Japanese Circulation Society¹⁰⁾ are to: (1) relieve ischemic clinical symptoms, (2) improve patency after revascularization, and (3) prevent cardiovascular events and thereby improve systemic prognosis, following the Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II consensus).¹¹⁾ Although antiplatelet agents have been confirmed to improve ischemic clinical symptoms in Japan, the overall rate of cardiovascular events in patients with ASO under treatment with antiplatelet agents has not been fully investigated in Japan.

Serotonin (5-hydroxytryptamine, 5-HT) released from activated platelets has various subtypes of receptors.¹²⁾ Serotonin mediates vasodilation by binding to 5-HT₁ receptors on endothelial cells and vasoconstriction as well as promoting platelet aggregation by binding to 5-HT_{2A} receptors on vascular smooth muscle cells and platelets,¹³⁻¹⁵⁾ resulting in regulation of a balance of vasodilation and vasoconstriction. In the injured endothelium, serotonin predominately binds to 5-HT_{2A} receptors, leading to vasoconstriction and platelet aggregation on vascular smooth muscle cells and platelets. Patients with ASO are reported to have higher plasma serotonin concentrations than those in healthy subjects.¹⁶⁾ Sarpogrelate hydrochloride, a selective 5-HT_{2A} antagonist, inhibits thrombus formation, suppresses platelet aggregation, and inhibits vascular smooth muscle cell proliferation.¹⁷⁻¹⁹⁾

The Surveillance of Cardiovascular Events in Arterio-Sclerosis Obliterans in Japan (SEASON) registry is an observational prospective cohort study for sarpogrelate hydrochloride (Anplag[®]), a 5-HT_{2A} receptor antagonist, in compliance with the GPSP Ministerial Ordinance of the Ministry of Health, Labour, and Welfare of Japan. The objectives of the study are to determine the prognosis of ASO patients receiving antiplatelet therapy, to explore the relationships between prognosis and the characteristics and risk factors of patients, and to compare the effectiveness of sarpogrelate in decreasing the event rate with those of other antiplatelet agents.

METHODS

Study design: The SEASON registry is a nationwide observational prospective cohort study with a two-year period of follow-up (Figure). Registration started in September 2009 and will end in September 2011. The study will be approved by the Ethics Review Board of each institution and patients will be enrolled after receiving an explanation about the study, if necessary.

Study population: Patients diagnosed with ASO by physicians and scheduled to undergo a long-term treatment with oral antiplatelet agents are eligible for enrollment in the SEASON registry. The inclusion criteria are shown in Table I. The diagnosis of ASO is confirmed with an ABPI or comparison of bilateral lower limb arteries by palpation. Patients are excluded from enrollment if any of the following criteria are met: 1) contraindications to the use of antiplatelet agents, such as hemorrhagic tendency and confirmed/possible pregnancy; and 2) inappropriateness for the study as determined by a patient's physician.

The SEASON registry will recruit approximately 10,000 patients and is designed to compile data from about 2,000 institutions across Japan. A broad range of physicians will be involved in the recruitment of eligible patients.

Antiplatelet agents: Physicians designate 1 antiplatelet agent as an “investigated drug,” which is newly administered at the time of enrollment, from among the following 6 oral antiplatelet agents: sarpogrelate, cilostazol, ticlopidine, prostaglandin I₂ (beraprost sodium), prostaglandin E₁ (limaprost alfadex), and eicosapentaenoic acid. All of these agents are approved for the treatment of ASO or TAO in Japan. No restrictions are placed on pretreatment with antiplatelet medication, or on concomitant use of antiplatelet agents. If antiplatelet agents other than the investigated drug, ie, aspirin, clopidogrel, and dipyridamole, are used, they are to be recorded as concomitant antiplatelet agents.

Sample size: The SEASON registry will recruit approximately 10,000 patients, consisting of 8,000 patients receiving sarpogrelate and 2,000 patients receiving other investigational drugs. The sample size will be determined based on two different points of view. First, in Japan, it is estimated based upon sales of each antiplatelet agent that about 590,000 ASO patients are being treated with antiplatelet agents. Of these, several tens of thousands of patients are estimated to initiate antiplatelet therapy or switch to other antiplatelet agents each year and we plan to enroll these patients. Second, we assume the incidence of the target population to be about 10%²⁰⁾ per two years and the precision of estimating incidence is targeted for 0.59 % or less.

It has been therefore determined that the study will be conducted in 10,000 such patients.

Patients receiving sarpogrelate and other “investigated drugs” will be sampled at a ratio of 4 to 1 at each institution.

Evaluations: At the time of registration, patients will be assessed at baseline for demographics, risk factors/comorbidities, premedication, current concomitant medications, medical history of ASO, Fontaine classification, severity of ischemic symptoms of lower extremities (coldness, numbness, intermittent claudication, rest pain, ulcer, and gangrene), laboratory values, intima media thickness (IMT), and endothelial function as shown in Table II. Ischemic symptoms are graded as: none, mild, moderate, or severe, ie, coldness and numbness are graded as: none, no episode experienced; mild, experienced the episode sometimes; moderate, experienced the episode almost everyday and annoying; and severe, having difficulty with routine daily activities. Intermittent claudication is graded as:

Figure. SEASON registry timeline.

Table I. Inclusion Criteria

Patients who meet both of the following criteria (1) and (2):
(1) Diagnosed with ASO and scheduled to receive long-term oral antiplatelet therapy.
(2) Not receiving sarpogrelate at the time of registration and meeting either of the following conditions:
· Scheduled to receive one of the antiplatelet agents under study.
· Scheduled to change to sarpogrelate or one of the other oral antiplatelet agents under study or to receive it in addition to antiplatelet therapy.

ASO indicates arteriosclerosis obliterans. Patients with history of ASO with previous vascular intervention and patients diagnosed based on ischemic symptoms of lower extremities will be included.

Table II. Evaluations at Baseline and 6-, 12-, 18-, and 24-Month Follow-Up Visits

Evaluation at baseline	Evaluation at follow-up
Demographics	Vascular events
Investigated antiplatelet agent	Revascularization
Pre-treatment, concomitant antiplatelet agents	Severity of ischemic symptoms, ABPI
Medical history of ASO	Global Improvement
Disease duration, Fontaine classification, ABPI, history of revascularization, amputation	Concomitant medications
Severity of ischemic symptoms	Laboratory values
Physical examination	eGFR, IMT, FMD
Waist circumference, blood pressure	Adverse events
Risk factors/comorbidity	Loss to follow-up
Hypertension, diabetes, hyperlipidemia, cardiovascular disease, cerebrovascular disease, chronic kidney disease	
Concomitant medications	
Antihypertensive agents, antidiabetic agents, antihyperlipidemic agents	
Laboratory values	
LDL cholesterol, HDL cholesterol, total cholesterol, triglycerides, HbA1c, serum creatinine or eGFR	
Others	
IMT, FMD (endothelial function)	

ASO indicates arteriosclerosis obliterans; ABPI, ankle brachial pressure index; PWV, pulse wave velocity; IMT, intima media thickness; FMD, flow-mediated dilation; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; HDL, high-density lipoprotein; and HbA1c, hemoglobin A1c.

none, able to walk more than 1 km; mild, initial claudication distance (ICD) is 500 m - < 1 km; moderate, ICD is 200 m - < 500 m; and severe, ICD is less than 200 m. Rest pain is graded as: none, no pain experienced; mild, experienced pain sometimes; moderate, need analgesics for pain; and severe, cannot sleep at night because of pain.²¹⁾

After registration, patients are followed every 6 months for a period of 2 years. At follow-up, cardiovascular events and changes in ischemic symptoms are evaluated. Every cardiovascular event will be reported at the time of onset.

Study outcomes: The study outcomes that will be evaluated are shown in Table III. The primary endpoint is a combination of cardiovascular events defined as follows: cerebrovascular events, including cerebral infarction, intracerebral hemorrhage,

subarachnoid hemorrhage, and transient ischemic attack (TIA); cardiovascular events, including acute myocardial infarction, unstable angina, and heart failure; and peripheral vascular events, including amputation, development of critical limb ischemia, acute limb ischemia, acute aortic dissection, rupture of an abdominal aortic aneurysm, acute pulmonary thromboembolism, and the new onset of end-stage renal failure.

Secondary endpoints are cerebrovascular events, cardiovascular events, peripheral vascular events, total cardiovascular death, fatal cerebrovascular events, fatal cardiovascular events, fatal peripheral vascular events, any cause of death, amputation, and development of critical limb ischemia. Changes from the baseline in the following are also examined: ischemic symptoms of lower extremities, global improvement of ischemic symptoms assessed by physicians, ABPI, estimated glomerular filtration rate (eGFR), and the safety of antiplatelet agents.

Study organization: The SEASON registry has a steering committee consisting of 7 members, who are responsible for ensuring the scientific validity of the study in terms of study design, statistical analysis, and publication.

All outcome events will be reported to the Efficacy Endpoint Review Committee, which will assess the appropriateness of the clinical judgment of cardiovascular events, with members of the Committee blind to any antiplatelet treatment. The Committee may request that physicians provide more clinical information for assessment, and any differences in opinion will be resolved by discussion.

The administrative office is located in the Post-Marketing Surveillance Department of Mitsubishi Tanabe Pharma Corporation, Osaka, Japan.

Primary and secondary hypotheses: The study will assess (1) the incidences of total cardiovascular events in patients with ASO receiving antiplatelet therapy, and (2) compare the effectiveness of sarpogrelate in decreasing the event rate with that of other “investigated drugs”, in the two populations defined below.

Distributions of concomitant diseases and other risk factors (Fontaine classification, ABPI, etc.) observed in ASO patients receiving antiplatelet agents will be evaluated quantitatively. In addition, the relationship between these factors and the incidence of total cardiovascular events will be analyzed. The profiles and prognoses of ASO patients receiving antiplatelet therapy in the real clinical world will be estimated.

SEASON may also provide a hypothesis with which to quantitatively compare the incidence of total cardiovascular events in patients treated with sarpogrelate or other antiplatelet agents. Improvements of clinical symptoms of ASO patients after treatment with antiplatelet agents will also be evaluated.

Data management: The SEASON registry implements an Electric Data Capture (EDC) system to register patients and collect patient data via the Internet. For security purposes, investigators receive their own ID and password to access the SEASON database after completing study participation. The data for a patient are electronically sent to the SEASON database and automatically exposed to edit checks at the time of data entry, and the system replies to queries to confirm discrepancies in data, unconfirmed missing data, implausible data, inconsistent data, typographical errors, and so on. Some investigators may choose to use a paper Case Report Form (CRF). In this case, data managers of the SEASON registry enter CRF

Table III. Evaluations at Baseline and 6-, 12-, 18-, and 24-Month Follow-Up Visits

A. Main outcome measures	
Primary endpoints	Secondary endpoints
Combined endpoint comprised of the following cardiovascular events; · Cerebrovascular events (including cerebral infarction, intracerebral hemorrhage, subarachnoidal hemorrhage, and TIA) · Cardiovascular events (including acute myocardial infarction, unstable angina, and heart failure) · Peripheral vascular events (including amputation, development of critical limb ischemia, acute limb ischemia, acute aortic dissection, rupture of an abdominal aortic aneurysm, acute pulmonary thromboembolism, and new onset of end-stage renal failure)	Cerebrovascular events Cardiovascular events Peripheral vascular events Total cardiovascular death Fatal cerebrovascular events Fatal cardiovascular events Fatal peripheral vascular events All causes of death Amputation Development of critical limb ischemia
B. Secondary outcomes measures	
Ischemic symptoms of lower extremities Global improvement of ischemic symptoms ABPI, eGFR, IMT, FMD Safety of antiplatelet agents	

TIA indicates transient ischemic attack; ABI, ankle brachial pressure index; PWV, pulse wave velocity; FMD, flow-mediated dilation; eGFR, estimated glomerular filtration rate; and IMT, intima media thickness.

data into the database and perform the same edit checks as the EDC. Cleaned data without discrepancies are locked electronically. A data manager of the SEASON registry is in charge of ensuring data quality.

Statistical analysis: The SEASON registry will quantitatively determine the incidence of total cardiovascular events in the Japanese population being treated with antiplatelet agents. Two main populations are being explored: (1) a “Real world population”, comprising patients clinically diagnosed as ASO by physicians; and (2) a “REACH-definition population”, comprising patients based on an ABPI < 0.9 and intermittent claudication, or history of lower limb revascularization.

General statistical approach: The mean, median, standard deviation, and range for continuous data and counts or percentages for categorical data will be calculated. A nonparametric approach will be applied to data exhibiting a nonnormal distribution. Relative risks represented by a hazard ratios and their 95% confidence intervals (CIs) will be calculated for the primary endpoint. Cox regression on time to events of patients with predefined cardiovascular events will be performed to test the impacts of covariates (treatment group with antiplatelet agents, history of ischemic events and/or related surgical operation, risk factors, patient characteristics, physician characteristics). Logistic regression on incident odds will also be performed in the same fashion. The level of significance is 0.05 and two-tailed. Two-sided CIs will be calculated.

Analysis yielding epidemiological findings: Descriptive analysis will be applied to patient characteristics and risk factors. Incident rates and proportions for high-risk groups, extracted based on risk factors, will be estimated. ABPI measurement,

Fontaine classification, and concomitant diabetes/ischemic heart diseases/cerebrovascular disease will be used when the high-risk group is extracted from the SEASON database.

Comparison of sarpgrelate with other antiplatelet agents: For each outcome, treatment groups will be sorted to sarpgrelate and other antiplatelet agents. For primary outcome, treatment groups will also be sorted by actual treatment groups taking into account the antiplatelet agents used concomitantly.

DISCUSSION

Currently in Japan, the total number of ASO patients is estimated to be 500,000-800,000, including 400,000 with symptomatic ASO.¹⁰⁾ We estimated the number of antiplatelet-treated ASO patients to be 590,000 as described above; a fairly large proportion of the ASO population is thus receiving antiplatelet therapy in Japan.

The SEASON registry will provide the first large database enabling epidemiological analysis regarding the cardiovascular events in ASO patients in Japan. As the sample size ($n = 10,000$) is much larger than that of the REACH registry ($n = 627$), more detailed analysis should be possible. Since the SEASON cohort includes Fontaine stage I patients who are considered to be asymptomatic in the guidelines, we are planning analyses using both a “real world population” to determine actual clinical status in Japan and a “REACH-definition population” to compare our patient profiles and prognoses with those of other studies.

One of our epidemiological interests is a comparison of the prognosis of asymptomatic and symptomatic ASO patients. Although a few studies have focused on this issue, their results have not been clear. After Crequi, *et al*²²⁾ demonstrated a tendency for symptomatic and severely symptomatic PAD patients to have a poorer prognosis than those with asymptomatic PAD, Leng, *et al*²³⁾ reported that the prognosis of asymptomatic patients was worse than that of symptomatic patients. Recently, the getABI Study Group revealed that both asymptomatic and symptomatic PAD had equally poor prognostic outcomes compared with subjects without PAD.²⁴⁾ The actual differences in prognosis between symptomatic and asymptomatic antiplatelet-treated ASO patients in Japan is expected to be clarified by comparison with the stratified SEASON cohort.

Another area of interest is the actual severities of disease in antiplatelet-treated ASO patients. Risk profiles and medication status should also be determinable. As reported in the one-year interim analysis of the REACH registry, patients who have cardiovascular and/or cerebrovascular disease, recognized as polyvascular disease, are considered at higher risk for cardiovascular events.⁷⁾ The prevalence of conventional risk factors, including diabetes, hypertension, hyperlipidemia, and chronic renal failure, and their relationship to prognosis are expected to be clarified. In addition, determination of changes in severity and risk profile over the two-year follow-up period is likely to be of significant value.

We believe our database can provide treatment strategies for controlling risk factors, which could help prevent the occurrence of cardiovascular events and exacerbation of ASO. In addition, SEASON may provide the opportunity to create the hypothesis that sarpgrelate prevents cardiovascular events. Preventing cardiovascular events is one of the aims of anti-

platelet therapy for ASO patients.¹⁰⁾

Although it is unclear whether the “investigated drugs” prevent cardiovascular events in ASO patients in Japan, cilostazol exhibited efficacy in secondary prevention of ischemic stroke in these patients.²⁵⁾ Origasa, *et al*²⁶⁾ demonstrated the prevention of cardiovascular events by beraprost in PAD patients in a meta-analysis of two foreign randomized controlled trials.^{27,28)} Eicosapentaenoic acid exhibited promising efficacy in preventing cardiovascular events in Japanese hypercholesterolaemic patients.²⁹⁾

Sarpogrelate, a selective 5-HT_{2A} receptor antagonist, inhibits serotonin-induced platelet aggregation, vasoconstriction, and vascular smooth muscle cell proliferation, and improves ischemic symptoms in ASO patients.^{30,31)} Recently, sarpogrelate has been found to have beneficial pleiotropic effects. First, it dilates preexistent collateral vessels, resulting in improvement of exercise capacity through increasing collateral circulation.³²⁾ Second, it improves endothelial function in ASO patients.³³⁾ Third, it retards the progression of atherosclerosis.³⁴⁾ Through these mechanisms, sarpogrelate exhibited efficacy comparable to that of aspirin in preventing cardiovascular events in patients with cerebral infarction.³⁵⁾ We are planning to compare the effectiveness and safety of sarpogrelate with those of other antiplatelet agents. Exploring adequate antiplatelet agents and concomitant pharmacotherapy for risk reduction could be of value for physicians who prescribe medication for ASO patients.

Limitations: Even though SEASON is a large, 10,000-patient, nationwide registry designed to explore cardiovascular events in ASO patients with antiplatelet agents, it has several limitations.

First, the study sites are not randomly sampled from all sites in which ASO patients are treated with antiplatelet platelets. This study has features both of an epidemiological investigation and an official post-marketing surveillance study. Since it involves post-marketing surveillance, only sites currently using sarpogrelate can participate. Second, patients are not to be consecutively recruited at each site. Third, the SEASON population consists of patients treated with antiplatelet agents, and includes neither nontreated patients nor healthy individuals. The prevalence of ASO in the general population thus cannot be estimated. Fourth, the sampling ratio of patients with sarpogrelate and other antiplatelet agents is 4 to 1, since one of the objectives of the present study is to focus on the favorable effectiveness of sarpogrelate on the total cardiovascular events in ASO patients. Finally, since this is an observational cohort study, some types of bias are unavoidable.

In summary, the SEASON registry represents a significant opportunity to increase our understanding of the incidence of total cardiovascular events in ASO patients on antiplatelet treatment in Japan. The results obtained are likely to offer an important opportunity to raise awareness of risk profiles and prognosis of patients with ASO over a wide range of physicians. The SEASON registry may also be able to create the hypothesis that sarpogrelate prevents cardiovascular events more effectively. SEASON may demonstrate the need for improvement in current clinical management strategies, and will provide a cross-sectional and longitudinal database. It can also serve as baseline data while physicians and public health practitioners in the ASO field work to improve the strategies for the prevention, detection, and treatment of ASO.

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