Stratification by Multidimensional Approach for Rational Treatment of Asymptomatic Carotid Stenosis (SMART-K Study): Study Protocol

Kazumichi YOSHIDA,¹ Susumu MIYAMOTO,¹ and SMART-K Study Group

¹Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, Kyoto, Japan

Abstract

With recent advances in medical treatments for carotid artery stenosis (CS), indications for carotid surgery should be more carefully considered for asymptomatic CS (ACS). Accurate stratification of ACS should be based on the risk of cerebral infarction, and subgroups of patients more likely to benefit from surgical treatment should be differentiated. Magnetic resonance imaging (MRI) offers a non-invasive, accurate modality for characterizing carotid plaque. Intraplaque hemorrhage (IPH) seems the most promising feature of vulnerable plaque detectable by MRI. Lectin-like oxidized low-density lipoprotein receptor-1 (LOX-1) is a type II membrane protein of the C-type lectin family with an extracellular domain that can be proteolytically cleaved and released as a soluble form (sLOX-1). This sLOX-1 plays a key role in the pathogenesis of atherosclerosis, and elevated sLOX-1 concentrations correlate with thin or ruptured fibrous caps in patients with acute coronary syndrome. This ongoing study aims to clarify the incidence of ischemic stroke in patients with ACS and IPH confirmed by MRI, and to assess whether sLOX-1 could provide a biomarker for risk of future ischemic events. The study population comprises patients with ACS (>60% area stenosis) associated with MRI-diagnosed IPH receiving follow-up under medical treatment. Primary endpoints comprise transient ischemic attack, stroke or amaurosis resulting from concerned CS. Secondary endpoints comprise any stroke or surgical treatment for progressive luminal stenosis. The target number of patients is 120 and the observational period is 36 months. The study results could help identify individuals with ACS who are refractory to medical therapy.

Key words: asymptomatic carotid artery stenosis, vulnerable plaque, intraplaque hemorrhage, biomarker

Introduction

Among the diseases causing ischemic cerebrovascular accidents, carotid artery stenosis reportedly accounts for approximately 20% of cases in Western countries.¹ There is concern that the rate of atherothrombotic cerebral infarction caused by arteriosclerosis (including carotid artery stenosis) may increase rapidly in Japan due to the Westernization of the country’s diet and the rapid aging of the population.

Conventionally, stenosis rate has been considered as the main indication for revascularization to treat carotid artery stenosis, based on the results of several overseas large-scale randomized clinical trials (RCTs).²⁻⁴ However, basic research on arteriosclerosis and new knowledge from clinical studies stemming from advances in diagnostic imaging have shown that the risk of ischemic events due to arteriosclerosis is not solely dependent on the stenosis rate, with the nature and shape of the atherosclerotic wall (plaque) also playing a prominent role.⁵

Another important change in the environment for determining indications for surgical treatment is the great improvement in the outcomes of medical treatment. Quitting smoking and other lifestyle improvements, as well as multimodal treatment for hypertension, diabetes, dyslipidemia, and other risk factors for generalized arteriosclerosis, have reduced the annual incidence of ischemic events in asymptomatic carotid artery stenosis to under 1% in recent years.⁶ This means that greater caution is now required in determining the indications for surgery, particularly for asymptomatic lesions, than was the case in the 1990s, when the results of RCTs demonstrating the superiority of carotid endarterectomy (CEA) over medical treatment were published.²⁻⁴
Important features of unstable plaque, which carries a high risk of causing ischemia, include intraplaque hemorrhage (IPH), high lipid-rich necrotic-core (LR-NC), and thinning/rupture of the fibrous cap. Of these, the state of the fibrous cap has been most strongly implicated in the risk of future ischemic events.7) The main diagnostic imaging modalities used to investigate the properties of carotid artery plaque are surface ultrasonography and magnetic resonance imaging (MRI). Although MRI of plaque offers high diagnostic accuracy for IPH among the above-mentioned indices of instability, wide inter-investigator variations exist in the non-invasive diagnostic imaging of LR-NC and the fibrous cap, and many issues remain to be resolved in actual clinical practice.8)

In terms of approaches to the assessment of unstable plaque other than diagnostic imaging, in the coronary artery field research is underway on serum biomarkers targeting a range of molecules associated with cardiomyopathy and inflammation in acute coronary syndrome (ACS). Soluble lectin-like oxidized low-density lipoprotein receptor 1 (sLOX-1) is a soluble receptor for oxidized low-density lipoprotein (LDL), known as the arteriosclerosis-inducing lipoprotein, and represents one such promising serum biomarker. This protein is specifically elevated in ACS, but not in patients with a healthy coronary artery or stable angina, and a validation study using optical coherence tomography demonstrated an association with thinning and rupture of the fibrous cap.9)

Advances in our understanding of the pathophysiology of arteriosclerosis are predicted to enable the incorporation of non-invasive investigations into the multifaceted diagnosis of carotid artery stenosis. This might enable more accurate stratification of ischemic risk, which would be of major clinical significance.

Purpose
The present study aims to clarify the outcomes of medical treatment for asymptomatic carotid artery stenosis with IPH, and to investigate the value of sLOX-1 in predicting high ischemic risk.

Materials and Methods

Overview
This is a multicenter prospective cohort study observing patients with asymptomatic carotid artery stenosis. Target enrollment is 120 patients during the 4-year enrollment period, and enrolled patients will be followed-up every 6 months for 3 years while receiving medical treatment. The study protocol has been approved by the Ethics Committee of the Graduate School and Faculty of Medicine of Kyoto University (approval number R0096). Patients who are candidates for study participation will be provided with oral and written explanations, and consent to participate in the study will be confirmed in writing before enrollment.

Selection criteria
Eligible patients are those who meet all the following criteria (Table 1):

1. Patients with asymptomatic atherosclerotic carotid artery stenosis with area stenosis of ≥60% as diagnosed by carotid artery ultrasonography, and who will be undergoing medical treatment. “Asymptomatic” is defined as no occurrence of cerebral infarction, transient ischemic attack, or amaurosis fugax resulting from carotid artery stenosis within 6 months before the date of enrollment.

2. Patients who have undergone MRI during the course of treatment, and in whom MRI plaque assessment has revealed the presence of IPH.

3. Patients who have provided sufficiently informed consent to participate in the study.

4. Patients who are capable of attending outpatient appointments and are expected to live ≥5 years after enrollment.

Exclusion criteria
Patients to whom any of the following apply will be excluded from the study (Table 1):

1. Patients who cannot undergo MRI.

Table 1  Inclusion and exclusion criteria

| Inclusion criteria | Exclusion criteria |
|--------------------|-------------------|
| 1. Medically treated asymptomatic patients with carotid artery stenosis with area stenosis of 60% as diagnosed by carotid artery ultrasonography. | 1. Contraindication for MRI. |
| 2. Presence of MRI-confirmed IPH. | 2. Irradiated neck. |
| 3. Confirmation of informed consent. | 3. Restenosis after CEA or CAS. |
| 4. Independent in ADL and with life expectancy more than 5 years. | 4. Patients judged by an investigator or subinvestigator to be ineligible for any other reason. |

ADL: activity of daily living, CAS: carotid artery stenting, CEA: carotid endarterectomy, IPH: intraplaque hemorrhage, MRI: magnetic resonance imaging.
(2) Patients who have previously undergone or are currently receiving radiotherapy to the head and neck region.

(3) Patients who have undergone CEA or carotid artery stenting for the carotid artery stenosis concerned.

(4) Patients judged by an investigator or subinvestigator to be ineligible for any other reason.

Parameters investigated

At enrollment Basic data on the following parameters will be collected from medical records and imaging investigations: (1) age and sex; (2) medical history (hypertension: blood pressure ≥140/90 mmHg during any examination from the previous 3 months, or taking antihypertensive medication; hypercholesterolemia: LDL cholesterol ≥140 mg/dL, or taking lipid-lowering medication; diabetes: hemoglobin A1c ≥6.1%, or taking oral blood sugar-lowering medication or insulin; cerebral infarction: diagnosed at a medical institution; ischemic heart disease: identification of coronary artery stenosis ≥75%, or previous treatment; atrial fibrillation: diagnosed at a medical institution; valve disease: diagnosed at a medical institution); (3) lifestyle (smoking: previous or current smoker; excessive alcohol consumption: alcohol intake ≥150 g/week); (4) blood tests (regular biochemistry tests and sLOX-1 antibody titer); and (5) cranial MRI: including diffusion-weighted imaging and fluid-attenuated inversion recovery imaging; (6) imaging evaluation of carotid artery stenosis (carotid artery ultrasonography, carotid artery MRI) (Table 2).

Follow-up investigations Examinations will be carried out every 6 months, and carotid artery ultrasound and carotid artery MRI every 12 months. Examinations, blood tests, carotid artery ultrasound, carotid artery MRI, and cranial MRI will be carried out until the end of the observation period or an endpoint is reached.

Carotid artery plaque imaging

Scanning conditions As long as MRI plaque imaging scanning for the diagnosis of IPH is carried out using T1-weighted imaging under the following conditions, the detailed parameters are not stipulated: (1) scans conducted on a 1.5-T device or better; (2) 3D scanning; (3) electrocardiogram gating not used; (4) inclusion of both short and long axes; and (5) follow-up scans conducted under identical scanning conditions to scanning at enrollment.

Diagnosis of IPH (definition of hyperintense plaque) Intraplaque hemorrhage is diagnosed if an arbitrary slice containing plaque contains a region of signal intensity ≥1.5 times that of neighboring sternocleidomastoid muscle (Fig. 1).

Rationale for target enrollment and follow-up period Among previous studies carried out in the US, a prospective observational study based on MRI plaque assessment of 50–79% asymptomatic carotid

![Fig. 1 Representative case of an asymptomatic patient with right carotid artery stenosis. He is a 61-year-old male and has a history of 3-year medical treatment for diabetes mellitus. Following diagnosis of asymptomatic right carotid artery low-grade stenosis with ultrasonography, he underwent carotid MRI plaque evaluation. T1-weighted image of his carotid artery demonstrated strikingly high signal plaque around the lumen (asterisk) compared with the adjacent sternocleidomastoid muscle (SCM) which indicated massive intraplaque hemorrhage. The T1 signal ratio of plaque to the SCM is 1.98 in this case. Multifaceted medical treatment with oral antihyperglycemic, antihypertensive and lipid-lowering drug has been continued in addition to the life-style modification.](image-url)
artery stenosis as diagnosed ultrasonographically found that ischemic events occurred in 14 of 154 participants during a mean 38.2 months of follow-up, and hazard ratios for patients with IHP or thinning/rupture of the fibrous cap on MRI plaque evaluation were 5.2 and 17.0, respectively. The interim report of an observational study of the natural course and treatment outcomes of asymptomatic carotid artery stenosis conducted in Japan (the CASTER Study) states that the rate of ischemic events in patients with asymptomatic lesions diagnosed ultrasonographically as ≥50% stenosis is 4.3%.

Approximately 30 ischemic events will be required to conduct multivariate analysis of the four factors of stenosis rate, expansive remodeling, maximum plaque wall thickness, and elevated sLOX-1. If the general rate of ischemic events in asymptomatic stenosis is taken as 3% per year and the hazard ratio of T1-hyperintensity (IPH) lesion is taken as 5, a 3-year observation of approximately 90 participants will be required. To take account of drop-outs, the required number of participants has been set as 120.

Endpoints

The primary endpoints are cerebral infarction, transient ischemic attack, or amaurosis fugax resulting from carotid artery stenosis, and the secondary endpoints are any cerebral infarction or any other condition that in the judgment of the attending physician requires revascularization (endarterectomy or stenting).

Data Analysis

Factors affecting ischemic events will be estimated using a method such as Cox's proportional hazard model. The occurrence of cerebral infarction, transient ischemic attack, or amaurosis fugax resulting from carotid artery stenosis will be estimated using the Kaplan–Meier method.

Discussion

With respect to the mechanisms whereby atherosclerotic vascular stenosis causes ischemic events, studies in the field of coronary artery disease since the 1980s have shown that not only the stenosis rate, but also plaque characteristics are important, with many cases of primary acute myocardial infarction (AMI) occurring due to plaque rupture in mild or moderate stenotic lesions. For carotid artery stenosis, it is now becoming clear that unstable plaque exhibiting severe inflammatory changes is closely associated with the risk of cerebral infarction. The stenosis rate was formerly considered the main indicator of ischemic risk, but with the emergence of new findings on the pathophysiology of carotid artery stenosis and awareness of the importance of unstable plaque, MRI plaque imaging, which has come into general use since the turn of the millennium, has come to play an important role.

One example of the importance of plaque characteristics in carotid artery stenosis is the existence of patients with mild stenosis (<50%), which according to the current US guidelines receives no benefit from CEA, who nevertheless exhibit an extremely high recurrence rate following multimodal medical treatment alone. The large-scale randomized trials in the 1990s established the efficacy of CEA and also provided the evidence used in formulating the above-mentioned guidelines that the risk of ischemic events as a result of mild stenosis is extremely low when the stenosis is treated medically. At that time, however, MRI arterial wall evaluation was not available, and non-stenotic lesions causing artery-to-artery embolism as a result of plaque rupture could conceivably have gone undiagnosed as carotid-artery-related cerebral infarction. This would have meant that those patients were never enrolled in those clinical trials in the first place. In light of the fact that some non-stenotic or mildly stenotic lesions nevertheless carry a high ischemic risk, and conversely that current multimodal medical treatment has reduced the annual incidence of events from asymptomatic lesions to below 1% despite the presence of moderate or severe stenosis, clear limitations exist to the treatment of carotid artery stenosis based on the assessment of stenosis rate alone.

Important features of unstable plaque that can be diagnosed by MRI include IPH, high LR-NC, and thinning/rupture of the fibrous cap. Of these, the state of the fibrous cap has been most strongly implicated in the risk of future ischemic events. However, although IPH can be diagnosed by MRI with a high degree of accuracy, many issues remain unresolved regarding the diagnostic imaging of LR-NC and the fibrous cap in actual clinical practice. LR-NC appears hypointense on T2-weighted imaging and is visualized as isointense or mildly hyperintense on T1-weighted imaging, but in addition to the wide signal range of LR-NC itself, a wide range of overlap with magnetic resonance signal values of other structural elements of plaque is also seen, reducing the diagnostic accuracy of non-contrast MRI compared with that for IPH.

The fibrous cap is visualized as a hypointense belt adjacent to the lumen on time-of-flight imaging.
and its thinning or rupture is diagnosed by the disruption of the belt-like structure of this hypointensity. However, this is difficult to evaluate in patients with severely stenotic lesions or irregular lumina, problems that are frequently encountered in everyday clinical practice. The wide inter-investigator variation represents another limitation. Recently, combined use of contrast MRI has improved diagnostic performance for LR-NC and the fibrous cap, but this entails the problem that the use of gadolinium increases the invasiveness of the procedure.\(^{16-18}\)

Among the molecular mechanisms known to cause plaque instability, including inflammatory changes in the vascular wall, enlargement of the LR-NC, thinning of the fibrous cap, and matrix metalloprotease activation, increased oxidative stress and oxidized LDL formation play an extremely important role.\(^{19}\)

Expression of the oxidized LDL receptor, LOX-1, is not homeostatic; LOX-1 is expressed in vascular endothelial cells in early-stage atherosclerotic lesions, and is strongly expressed in macrophages and smooth muscle cells inside the plaque in advanced lesions. LOX-1 mediates the uptake of oxidized LDL, causing various inflammatory changes in the process leading up to plaque rupture. In this process, the extracellular domain is cleaved by protease activity and released into the blood as sLOX-1.\(^{20}\)

Serum concentrations of sLOX-1 are elevated as a result of the upregulated expression of LOX-1 and local protease activity in the acute phase of ACS,\(^{21}\) and optical coherence tomographic studies of patients with acute ACS have identified sLOX-1 as a serum biomarker for the diagnosis of thinning/rupture of the fibrous cap with high sensitivity and specificity.\(^{39}\) Unlike troponin T and I, which reflect previous myocardial damage due to AMI and are already used in the clinical treatment of coronary artery disease, sLOX-1 is elevated before and immediately after rupture of the fibrous cap, and thus provides a marker for assessing the stage preceding ischemic tissue damage. This suggests potential utility for predicting onset and extremely early diagnosis.

**Study limitations**

Multimodal evaluation with a combination of non-contrast MRI plaque imaging and blood test markers enabling accurate stratification of ischemic risk would be extremely valuable in clinical terms. However, the present study has several inherent limitations, as follows. (1) Because the annual incidence of ischemic events resulting from asymptomatic carotid artery stenosis in general is extremely low, limitations on the number of patients who can be enrolled in the present study mean that the study population must be restricted to patients with IPH, which carries a high risk of ischemic events. Large-scale longitudinal studies of all asymptomatic patients over a long period will be required in future to identify indices for true ischemic risk stratification. (2) The study endpoint is symptomatic cerebral infarction. Depending on the location of the ischemia, however, even cerebral infarctions of some size may sometimes appear asymptomatic at first glance. Endpoints must therefore be determined on an imaging basis in order to clarify the association between plaque characteristics and the risk of ischemic events in detail. In practice, however, carrying out MRIs with sufficient frequency to catch all asymptomatic infarctions is unrealistic. (3) As mentioned above, the potential of sLOX-1 as a biomarker for predicting ischemic events is based on the results of studies of coronary artery disease in ACS patients. No study has yet addressed the association between sLOX-1 and risk of ischemic events in carotid artery stenosis. In the sense of predicting future ischemic risk, whether sLOX-1 is elevated when the fibrous cap has thinned but has not yet ruptured remains unclear at this point.

**State of progress**

Screening by the ethics committees of all the participating institutions has been completed, and enrollment has started. At the time this paper was submitted, 67 patients were under observation.

**Acknowledgments**

I. SMART-K study group

Susumu Miyamoto, Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Jun C Takahashi, Division of Neurosurgery, National Cerebral and Cardiovascular Center, Osaka, Japan.

Kazunori Toyoda, Division of Cerebrovascular Medicine and Neurology, National Cerebral and Cardiovascular Center, Osaka, Japan.

Koichi Iwasaki, Department of Neurosurgery, Kitano Hospital, Osaka, Japan.

Masaki Uno, Department of Neurosurgery, Kobe City Medical Center General Hospital, Hyogo, Japan.

Nobuyuki Sakai, Department of Neurosurgery, Kobe City Medical Center General Hospital, Hyogo, Japan.

Masaaki Uno, Department of Neurosurgery, Kawasaki Medical School, Okayama, Japan.

Yoshiki Yagita, Department of Stroke Medicine, Kawasaki Medical School, Okayama, Japan.

Masaki Chin, Department of Neurosurgery, Kurashiki Central Hospital, Okayama, Japan.
Koji Iihara, Department of Neurosurgery, Kyusyu University Graduate School of Medical Sciences, Fukuoka, Japan.
Yasushi Okada, Stroke Center, Kyusyu Medical Center, Fukuoka, Japan.
Taketo Hatano, Department of Neurosurgery, Kokura Memorial Hospital, Fukuoka, Japan.
Tsuyoshi Ota, Department of Neurosurgery, Kochi Health Sciences Center, Kochi, Japan

II. Neuroradiological study committee
Tomohisa Okada, Department of Human Brain Research Center, Kyoto University Graduate School of Medicine, Kyoto, Japan.
Yasutaka Fushimi, Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan.

Financial Support
This research was partially supported by the Ministry of Education, Science, Sports and Culture, Grant-in-Aid for Scientific Research(C), 2015-2018 (15K10299, Kazumichi Yoshida).

Conflicts of Interest Disclosure
All authors have no conflicts of interest.

References
1) Petty GW, Brown RD, Whisnant JP, Sicks JD, O’Fallon WM, Wiebers DO: Ischemic stroke subtypes: a population-based study of incidence and risk factors. Stroke 30: 2513–2516, 1999
2) Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 351: 1379–1387, 1998
3) Walker MD, Marler JR, Goldstein M, et al.: Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 273: 1421–1428, 1995
4) North American Symptomatic Carotid Endarterectomy Trial Collaborators, Barnett HJM, Taylor DW, et al.: Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 325: 445–453, 1991
5) Naghavi M, Libby P, Falk E, et al.: From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 108: 1664–1672, 2003
6) Abbott AL: Medical (nonsurgical) intervention alone is now best for prevention of stroke associated with asymptomatic severe carotid stenosis: results of a systematic review and analysis. Stroke 40: e573–e583, 2009
7) Gupta A, Baradaran H, Schweitzer AD, et al.: Carotid plaque MRI and stroke risk: a systematic review and meta-analysis. Stroke 44: 3071–3077, 2013
8) Saba L, Yuan C, Hatsuakami TS, et al.: Carotid artery wall imaging: perspective and guidelines from the ASNR Vessel Wall Imaging Study Group and expert consensus recommendations of the American Society of Neuroradiology. AJNR Am J Neuroradiol 39: E9–E31, 2018
9) Kobayashi N, Takano M, Hata N, et al.: Soluble lectin-like oxidized LDL receptor-1 (sLOX-1) as a valuable diagnostic marker for rupture of thin-cap fibroatheroma: verification by optical coherence tomography. Int J Cardiol 168: 3217–3223, 2013
10) Hackett D, Davies G, Maseri A: Pre-existing coronary stenoses in patients with first myocardial infarction are not necessarily severe. Eur Heart J 9: 1317–1323, 1988
11) Brinjikji W, Huston J, Rabinstein AA, Kim GM, Lerman A, Lanzino G: Contemporary carotid imaging: from degree of stenosis to plaque vulnerability. J Neurosurg 124: 27–42, 2016
12) Yuan C, Mitsumori LM, Ferguson MS, et al.: In vivo accuracy of multispectral magnetic resonance imaging for identifying lipid-rich necrotic cores and intraplaque hemorrhage in advanced human carotid plaques. Circulation 104: 2051–2056, 2001
13) Yuan C, Kerwin WS, Ferguson MS, et al.: Contrast-enhanced high resolution MRI for atherosclerotic carotid artery tissue characterization. J Magn Reson Imaging 15: 62–67, 2002
14) Brott TG, Halperin JL, Abbara S, et al.: 2011 ASA/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary. A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neurology, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Circulation 124: 489–532, 2011
15) Hatsuakami TS, Ross R, Polissar NL, Yuan C: Visualization of fibrous cap thickness and rupture in human atherosclerotic carotid plaque in vivo with high-resolution magnetic resonance imaging. Circulation 102: 959–964, 2000
16) Cai J, Hatsuakami TS, Ferguson MS, et al.: In vivo quantitative measurement of intact fibrous cap and lipid-rich necrotic core size in atherosclerotic carotid plaque: comparison of high-resolution, contrast-enhanced magnetic resonance imaging and histology. Circulation 112: 3437–3444, 2005
17) Wasserman BA, Smith WI, Trout HH, Cannon RO, Balaban RS, Arai AE: Carotid artery atherosclerosis: in vivo morphologic characterization with gadolinium-enhanced double-oblique MR imaging initial results. Radiology 223: 566–573, 2002

18) Rogosnitzky M, Branch S: Gadolinium-based contrast agent toxicity: a review of known and proposed mechanisms. Biometals 29: 365–376, 2016

19) Hansson GK: Inflammation, atherosclerosis, and coronary artery disease. N Engl J Med 352: 1685–1695, 2005

20) Murase T, Kume N, Kataoka H, et al.: Identification of soluble forms of lectin-like oxidized LDL receptor-1. Arterioscler Thromb Vasc Biol 20: 715–720, 2000

21) Hayashida K, Kume N, Murase T, et al.: Serum soluble lectin-like oxidized low-density lipoprotein receptor-1 levels are elevated in acute coronary syndrome: a novel marker for early diagnosis. Circulation 112: 812–818, 2005

Address reprint requests to: Kazumichi Yoshida, MD, PhD, Department of Neurosurgery, Kyoto University Graduate School of Medicine, 54 Kawahara-cho, Shogoin, Sakyoku, Kyoto, Kyoto 606-8507, Japan. e-mail: kazuy@kuhp.kyoto-u.ac.jp