Prevalence of Coronary Artery Disease in Japanese Patients With Cerebral Infarction

— Impact of Metabolic Syndrome and Intracranial Large Artery Atherosclerosis —

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Background Patients with cerebral infarction have a high prevalence of asymptomatic coronary artery disease (CAD) and other vascular diseases, but there is a lack of such data for Japanese patients, so the present study investigated the prevalence of cardiovascular disease (CVD) in Japanese patients and determined the predictors of CAD.

Methods and Results The study group comprised 104 patients with cerebral infarction who had no history of CVD. All patients underwent coronary computed tomographic angiography, and systematic evaluation was done on the basis of the presence of other vascular diseases, CVD risk markers, and the degree of atherosclerosis. Of the total, 39 patients (37.5%) had CAD, 9 (8.7%) had carotid artery stenosis, 9 (8.7%) had peripheral artery disease of the lower limbs, and 3 (2.9%) had atherosclerotic renal artery stenosis. Multiple regression analysis showed that the presence of CAD was independently associated with metabolic syndrome (odds ratio (OR) 5.008, 95% confidence interval (CI) 1.538–16.309; $p < 0.01$) and intracranial large artery atherosclerosis (OR 4.979, 95% CI 1.633–15.183; $p < 0.01$).

Conclusion Japanese patients with cerebral infarction have a high prevalence of CVD, especially asymptomatic CAD. Both metabolic syndrome and intracranial large artery atherosclerosis may be potential predictors for identifying patients with cerebral infarction who are at the highest risk of asymptomatic CAD. (*Circ J* 2008; 72: 404–408)

Key Words: Cerebral infarction; Computed tomography; Coronary artery disease; Magnetic resonance imaging; Metabolic syndrome

Atherosclerosis is a widespread disorder involving various arterial territories and it is a progressive disease process. Compared with the general population, patients with cerebral infarction have an increased risk of death, notably from coronary artery disease (CAD)! In addition, patients with cerebral infarction die more frequently from CAD than from recurrent cerebral infarction or other neurological diseases.^{2–4}

There is a racial difference in the sites of prevalence for atherosclerotic lesions. Asian people have been shown to have more severe intracranial vascular lesions, whereas Western people have more severe extracranial lesions⁵ and there is a strong correlation between the extent of coronary atherosclerosis and extracranial carotid atherosclerosis^{6–8}. In Japan, adoption of a Westernized lifestyle has caused an

increase in extracranial carotid artery disease and CAD^{9,10} so for patients with cerebral infarction it is important to prevent not only intracranial recurrence but also other cardiovascular events. Screening for CAD could potentially improve prognoses, as several studies of patients with asymptomatic ischemia suggest that medical treatment and revascularization alter prognoses to an extent beyond risk factor reduction.¹¹

The main objective of the present study was to estimate the prevalence of cardiovascular disease (CVD) in Japanese patients hospitalized for cerebral infarction. The secondary objective was to elucidate the predictors of asymptomatic CAD.

Methods

Study Population

We investigated 243 consecutive patients who were admitted between May 2005 and March 2007 because of a first cerebral infarction. Diagnosis of cerebral infarction was based on sudden onset of loss of global or focal cerebral function persisting for >24 h, as well as findings from computed tomography or magnetic resonance imaging. Patients were excluded if they fulfilled 1 or more of the following criteria: (1) history of clinical CVD, (2) atrial fibrillation, (3) age ≥ 80 years, (4) modified Rankin scale ≥ 4 , (5) dementia, and (6) renal insufficiency (defined as serum

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Fig 1. Prevalence of cardiovascular diseases and the number of revascularization cases in 104 Japanese patients with cerebral infarction.

creatinine ≥ 1.6 mg/dl). Of the 107 patients enrolled, 3 were excluded because of inadequate images from coronary computed tomographic angiography (CTA). Informed consent was given by all participants and the study protocol was approved by the hospital's ethics committee.

Definitions of Cardiovascular Risk Factors

The listed cardiovascular risk factors were hypertension, diabetes mellitus, hypercholesterolemia, current smoking, and metabolic syndrome. Blood samples following an overnight fast were obtained from all patients. Hypertension was defined as $\geq 140/90$ mmHg or current treatment with anti-hypertensive drugs. Diabetes mellitus was defined as a fasting blood glucose level ≥ 126 mg/dl and/or a glycosylated hemoglobin level $\geq 6.5\%$, or treatment with insulin or oral antidiabetic drugs. Hypercholesterolemia was defined as a low-density lipoprotein C level ≥ 140 mg/dl or current treatment with lipid-lowering drugs. The presence or absence of a smoking history was determined by a standardized self-administered questionnaire. Metabolic syndrome was defined according to the 2005 definition and diagnostic criteria for Japanese: waist circumference ≥ 85 cm for men or ≥ 90 cm for women as an essential component combined with 2 or more of the following components: triglycerides ≥ 150 mg/dl and/or high-density lipoprotein C < 40 mg/dl; systolic blood pressure (BP) ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg; fasting blood glucose ≥ 110 mg/dl.

Ultrasound Examination

B-mode ultrasound of the carotid arteries was performed using a high-resolution ultrasound machine (HDI5000 ATL, Philips Medical Systems, Andover, MA, USA) and a 5–12-MHz linear array transducer. All examinations were carried out by sonographers who were unaware of the clinical data. The scanning protocol was in accordance with that of Allan et al.¹²

Table 1 Clinical Characteristics of the Study Group

Age (years)	65.9 $\pm$ 10.6
Gender (M/F)	76/28
BMI (kg/m ²)	23.8 $\pm$ 3.1
Waist circumference (cm)	85.4 $\pm$ 7.6
Type of cerebral infarction	
Lacunar	66.4%
Atherothrombotic	9.6%
Cardioembolic	16.3%
Other	7.7%
Laboratory data	
Fasting plasma glucose, mg/dl	123 $\pm$ 49
LDL-cholesterol, mg/dl	132.3 $\pm$ 34.7
HDL-cholesterol, mg/dl	48.8 $\pm$ 14.3
Triglycerides, mg/dl	136.6 $\pm$ 69.4
Hemoglobin A _{1c} , %	6.6 $\pm$ 1.8
Cardiovascular risk factors	
Hypertension	51.9%
Hypercholesterolemia	45.2%
Diabetes mellitus	36.5%
Smoking	37.5%
>2 risk factors	23.1%
Metabolic syndrome	38.5%

BMI, body mass index; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Measurement of Arterial Pressure and Velocity Indices

The ankle–brachial pressure index (ABI) and brachial–ankle pulse wave velocity (baPWV) measurements were performed using the oscillometric method. After the patient had rested supine for >5 min, the baPWV was measured with a volume-plethysmograph (FORM/ABI, Colin Co Ltd, Komaki, Japan) while the subject was in the same position. This instrument simultaneously records the baPWV and the brachial and ankle BPs on the left and right sides, produces an electrocardiogram (ECG), and records the heart sounds. The lowest ABI value and the highest baPWV for the left and right sides were determined. This method has been validated elsewhere.¹³

Definitions of CVDs

CAD was defined as stenosis $\geq 50\%$ as shown on coronary CTA, during which routine premedication with β -blockers, 20–60 mg metoprolol for lowering the heart rate, and oral nitroglycerine spray were used. ECG-gated coronary CTA studies were performed with a 8-MDCT scanner (Light Speed Ultra with Xstream, GE Healthcare, Milwaukee, MI, USA). The following imaging and reconstruction parameters were used: detector collimation, 8×1.25 mm; kVp, 120; mAs, 300; pitch, 0.125; rotation time, 0.5 s; slice width, 1.25 mm. We continuously injected 80 ml of non-ionic iodinated contrast material (Iopamiron [iopamidol], 300 mgI/ml, Schering) at a rate of 3.0 ml/s using a power injector. The postprocessing reformations were performed on an Advantage Workstation 4.2 (GE Healthcare). A cardiologist who was unaware of the clinical data evaluated the coronary CTA images in consensus, using a modified American College of Cardiology/American Heart Association (ACC/AHA) classification that included all segments 2 mm or greater in diameter belonging to the left main, left anterior descending, left circumflex, and right coronary arteries.

Intracranial large artery atherosclerosis was defined as visual stenosis or irregularities on magnetic resonance angiography (MRA), which was performed using a 1.5-T magnetic resonance system (Intera 1.5T, Philips Medical Systems). We used a 3-dimensional time-of-flight gradient-

Table 2 Univariate Analysis of CAD and Other Vascular Diseases

	CAD (+)	CAD (−)	p value
n	39	65	
Intracranial large artery atherosclerosis*	24/34	17/57	<0.001
Other vascular diseases	8	8	0.26
PAD of the lower limbs	4	5	0.65
Carotid artery stenosis	5	4	0.24
ARAS	2	1	0.29

*Thirteen patients' data were not obtained.

CAD, coronary artery disease; PAD, peripheral artery disease; ARAS, atherosclerotic renal artery stenosis.

Table 3 Univariate Analysis of Clinical Data of Patients With Cerebral Infarction

	CAD (+)	CAD (−)	p value
n	39	65	
Age (years)	65.8±7.2	66.0±12.2	0.90
Gender (M/F)	31/8	45/20	0.25
BMI (kg/m ²)	24.0±2.7	23.6±3.3	0.60
Waist circumference (cm)	86.1±7.6	85.0±7.7	0.58
Type of cerebral infarction			0.95
Lacunar	69.2%	64.6%	
Atherothrombotic	7.7%	10.8%	
Cardioembolic	15.4%	16.9%	
Other	7.7%	7.7%	
Cardiovascular risk factors			
Hypertension	51.3%	52.3%	0.92
Hypercholesterolemia	46.2%	44.6%	0.88
Diabetes mellitus	51.3%	27.7%	0.016
Smoking	53.8%	27.7%	0.008
≥2 risk factors	35.9%	15.4%	0.0016
Metabolic syndrome	64.1%	23.1%	<0.0001
ABI	1.05±0.18	1.11±0.11	0.060
baPWV	2,268±595	2,053±443	0.053
IMT	1.59±0.63	1.46±0.62	0.29

ABI, ankle-brachial pressure index; baPWV, brachial-ankle pulse wave velocity; IMT, intima-media thickness. Other abbreviations see in Tables 1, 2.

echo technique for the intracranial arteries. The intracranial portion of the internal carotid artery, the anterior, middle, posterior cerebral arteries, and basilar artery were evaluated by a radiologist who was unaware of the clinical data.

Carotid artery stenosis was assessed by duplex ultrasonography and defined as stenosis ≥50% as calculated by ECST criteria (the residual luminal diameter divided by the normal diameter of the artery at that level).

Peripheral artery disease (PAD) of the lower limbs was defined as ABI <0.9. Atherosclerotic renal artery stenosis (ARAS) was defined as stenosis ≥50% as demonstrated by CTA or conventional angiography and the additional presence of resistant hypertension.¹⁴

Statistical Analysis

All descriptive data are expressed as the mean value±SD or the number of patients (percentage). Continuous variables were compared by Student's unpaired t-test. The chi-square test was used for categorical data. To identify predictors of asymptomatic CAD, multivariate logistic regression analyses were used. Univariate variables with p<0.20 were entered into the multivariate logistic models. A value of p<0.05 with 95% confidence interval was considered significant. All statistical analyses were performed using commercially available statistical software (StatView version 5.0, SAS Institute Inc, Cary, NC, USA).

Results

Prevalence of CVDs and Clinical Features

The prevalence of CVDs and the clinical characteristics for all 104 patients are summarized in Fig 1 and Table 1, respectively. We were not able to obtain the MRA images for 13 patients; 41 patients (45.1%) had intracranial large artery atherosclerosis; 39 patients (37.5%) had CAD and of them 20 (19.2%) and 12 (11.5%) underwent invasive coronary angiography or percutaneous coronary interventions (PCIs), respectively, because of significant stenosis. Nine patients (8.7%) had carotid artery stenosis and 3 (2.9%) underwent carotid artery stenting. Nine patients (8.7%) had PAD of the lower limbs and 3 (2.9%) underwent revascularization (2 by percutaneous transluminal angioplasty, 1 by operation). Three patients (2.9%) had ARAS and 1 (1.0%) underwent percutaneous transluminal renal angioplasty.

The relationship between asymptomatic CAD and other vascular diseases was analyzed (Table 2). Compared with patients without CAD, those with CAD had a higher prevalence of intracranial large artery atherosclerosis (70.6% vs 29.8%). Between these 2 groups, however, there was no difference in the prevalence of other vascular diseases such as carotid artery stenosis, PAD of the lower limbs, or ARAS. Patients with CAD also had a higher incidence of diabetes mellitus (51.3 vs 27.7%), smoking (53.8 vs 27.7%), the presence of ≥2 risk factors (35.9% vs 15.4%), and metabolic syndrome (64.1 vs 23.1%). Intima-media thickness (IMT) and pulse wave velocity values were high but not signifi-

Table 4 Multivariate Analysis of the Prevalence of Asymptomatic CAD in Patients With Cerebral Infarction

	OR	95% CI	p value
Metabolic syndrome	5.008	1.538–16.309	0.0075
Diabetes mellitus	0.653	0.145–2.947	0.58
Smoking	2.245	0.687–7.336	0.18
≥2 risk factors	1.125	0.224–5.647	0.89
ABI	0.079	0.001–8.158	0.28
baPWV	1.000	0.999–1.001	0.99
Intracranial large artery atherosclerosis	4.979	1.633–15.183	0.0048

OR, odds ratio; CI, confidence interval. Other abbreviations see in Tables 2,3.

cantly different between groups, as shown in Table 3.

Predictors for Asymptomatic CAD

Variables with $p < 0.20$ on univariate logistic regression analysis included diabetes mellitus, smoking, the presence of ≥ 2 risk factors, metabolic syndrome, ABI, baPWV, and intracranial large artery atherosclerosis. These factors were then entered into the multivariate logistic model, which showed that metabolic syndrome and intracranial large artery atherosclerosis were independent predictors of asymptomatic CAD in patients with cerebral infarction (Table 4).

Discussion

There are no previous reports regarding Japanese patients with cerebral infarction or their evaluation by coronary CTA and the present study showed that 37.5% (39 of 104) of Japanese patients with cerebral infarction had asymptomatic CAD. Small studies have suggested that 23–58% of stroke patients without clinical CAD may have asymptomatic myocardial ischemia, as determined by exercise ECG or stress myocardial scintigraphy^{15–18} but Japanese people are considered to have CAD less frequently than Western people.¹⁹ However, our study showed a similar frequency to other studies of Western populations and although the high incidence may be partially attributed to a CAD definition of $\geq 50\%$ stenosis, rather than $\geq 75\%$, we can say that Japanese patients with cerebral infarction have as high a risk of asymptomatic CAD as Western patients.

Multivariate analysis showed that metabolic syndrome and intracranial large artery atherosclerosis were independently associated with asymptomatic CAD in patients with cerebral infarction. Metabolic syndrome is a cluster of specific CVD risk factors, including obesity, impaired glucose regulation, dyslipidemia, and hypertension. Its underlying pathophysiology is thought to be related to insulin resistance.²⁰ Many studies have shown that patients diagnosed with metabolic syndrome have a higher prevalence of CAD.^{20,21} In addition, hypertension, hypercholesterolemia, diabetes mellitus, and smoking have been long known as major cardiovascular risk factors and patients with multiple risk factors have a higher risk of CAD than patients with a single risk factor.²² The present study showed that metabolic syndrome is a better predictive marker of asymptomatic CAD in patients with cerebral infarction than every major risk factor either individually or in combination.

Atherosclerosis is a systemic disorder in which disease in one vascular bed reflects disease in other vascular beds.²³ Intracranial large artery atherosclerosis²⁴ IMT of the common carotid artery,^{25–27} ABI,^{13,27–30} and baPWV^{13,31,32} have all been reported to be associated with CAD. In the present study, only intracranial large artery atherosclerosis was an independent predictor of asymptomatic CAD in patients

with cerebral infarction. Increased IMT and baPWV are common among patients with cerebral infarction, and are therefore not significantly associated with CAD, but may be useful markers of the early stage of CVD.¹³ The ABI value was also not associated with CAD, possibly because the association between the ABI value and CVD is U-shaped and not inversely proportional.³³ Additionally, only 9 of the present patients had a low ABI (< 0.9), which is generally associated with a much more advanced stage of CVD.^{34,35}

Whether stroke patients should be investigated for asymptomatic CAD remains a matter of debate! Screening for asymptomatic CAD could potentially improve prognoses,³⁶ because several studies of patients with asymptomatic ischemia suggest that medical therapy³⁷ or revascularization^{1,38–40} alter prognoses to an extent beyond risk factor reduction. Noninvasive screening for asymptomatic CAD in all patients with cerebral infarction may not be cost-effective, so it is essential to distinguish high-risk patients who will benefit most from CAD screening. In patients without any previous history of clinical CAD at the time of stroke, however, a meta-analysis was unable to estimate the risk of myocardial infarction and cardiac death,¹¹ which highlights the urgency of developing a new screening strategy for secondary prevention. Our study results suggest that metabolic syndrome and intracranial large artery atherosclerosis are factors that may help distinguish patients with cerebral infarction who are at a higher risk of asymptomatic CAD.

Study Limitations

The number of study patients was small, so a large multicenter study is required to confirm the predictors of complicating asymptomatic CAD. The long-term benefits of detecting CAD in patients with cerebral infarction also cannot be elucidated from this study. A follow-up of a large cohort is required to determine effects on morbidity and mortality.

Conclusion

The present study showed that 37.5% of Japanese patients with cerebral infarction and no history of CAD had asymptomatic CAD. From the viewpoint of cost-effectiveness, selective screening based on risk stratification is required. The present study results suggest that metabolic syndrome and intracranial large artery atherosclerosis, as determined by MRA, may be potential markers of patients with cerebral infarction who are at the highest risk for asymptomatic CAD.

References

- Adams RJ, Chimowitz MI, Alpert JS, Awad IA, Cerqueria MD, Fayad P, et al. Coronary risk evaluation in patients with transient ischemic attack and ischemic stroke: A scientific statement for health-

- care professionals from the Stroke Council and the Council on Clinical Cardiology of the American Heart Association/American Stroke Association. *Circulation* 2003; **108**: 1278–1290.
2. Toole JF, Yusem CP, Janeway R, Johnston F, Davis C, Cordell AR, et al. Transient ischemic attacks: A prospective study of 225 patients. *Neurology* 1978; **28**: 746–753.
 3. Graor RA, Hetzer NR. Management of coexistent carotid artery and coronary artery disease. *Stroke* 1988; **19**: 1441–1444.
 4. Hartmann A, Rundek T, Mast H, Paik MC, Boden-Albala B, Mohr JP, et al. Mortality and causes of death after first ischemic stroke: The Northern Manhattan Stroke Study. *Neurology* 2001; **57**: 2000–2005.
 5. Nishimaru K, McHenry LC Jr, Toole JF. Cerebral angiographic and clinical differences in carotid system transient ischemic attacks between American Caucasian and Japanese patients. *Stroke* 1984; **15**: 56–59.
 6. Howard G, Ryu JE, Evans GW, McKinney WM, Toole JF, Murros KE, et al. Extracranial carotid atherosclerosis in patients with and without transient ischemic attacks and coronary artery disease. *Arteriosclerosis* 1990; **10**: 714–719.
 7. Crouse JR, Harpold GH, Kahl FR, Toole JF, McKinney WM. Evaluation of a scoring system for extracranial carotid atherosclerosis extent with B-mode ultrasound. *Stroke* 1986; **17**: 270–275.
 8. Craven TE, Ryu JE, Espeland MA, Kahl FR, McKinney WM, Toole JF, et al. Evaluation of the associations between carotid artery atherosclerosis and coronary artery stenosis: A case–control study. *Circulation* 1990; **82**: 1230–1242.
 9. Komachi Y, Tanaka H, Shimamoto T, Handa K, Iida M, Isomura K, et al. A collaborative study of stroke incidence in Japan: 1975–1979. *Stroke* 1986; **15**: 28–36.
 10. Shimamoto T, Komachi Y, Inada H, Doi M, Iso H, Sato S, et al. Trends for coronary heart disease and stroke and their risk factors in Japan. *Circulation* 1989; **79**: 503–515.
 11. Touzé E, Varenne O, Chatellier G, Peyrard S, Rothwell PM, Mas JL. Risk of myocardial infarction and vascular death after transient ischemic attack and ischemic stroke: A systematic review and meta-analysis. *Stroke* 2005; **36**: 2748–2755.
 12. Allan PL, Mowbray PI, Lee AJ, Fowkes FG. Relationship between carotid intima-media thickness and symptomatic and asymptomatic peripheral arterial disease: The Edinburgh Artery Study. *Stroke* 1997; **28**: 348–353.
 13. Koji Y, Tomiyama H, Ichihashi H, Nagae T, Tanaka N, Takazawa K, et al. Comparison of ankle-brachial pressure index and pulse wave velocity as markers of the presence of coronary artery disease in subjects with a high risk of atherosclerotic cardiovascular disease. *Am J Cardiol* 2004; **94**: 868–872.
 14. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 report. *JAMA* 2003; **21**: 2560–2572.
 15. Rokey R, Rolak LA, Harati Y, Kutka N, Verani MS. Coronary artery disease in patients with cerebrovascular disease: A prospective study. *Ann Neurol* 1984; **16**: 50–53.
 16. Di Pasquale G, Pinelli G, Grazi P, Andreoli A, Corbelli C, Manini GL, et al. Incidence of silent myocardial ischemia in patients with cerebral ischemia. *Eur Heart J* 1988; **9**(Suppl N): 104–107.
 17. Chimowitz MI, Poole RM, Starling MR, Schwaiger M, Gross MD. Frequency and severity of asymptomatic coronary disease in patients with different causes of stroke. *Stroke* 1997; **28**: 941–945.
 18. Arenillas JF, Candell-Riera J, Romero-Farina G, Molina CA, Chacón P, Aguadé-Bruix S, et al. Silent myocardial ischemia in patients with symptomatic intracranial atherosclerosis: Associated factors. *Stroke* 2005; **36**: 1202–1206.
 19. Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project: Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994; **90**: 583–612.
 20. Saely CH, Aczel S, Marte T, Langer P, Hoeffle G, Drexel H. The metabolic syndrome, insulin resistance, and cardiovascular risk in diabetic and nondiabetic patients. *J Clin Endocrinol Metab* 2005; **90**: 5698–5703.
 21. Eberly LE, Prineas R, Cohen JD, Vazquez G, Zhi X, Neaton JD, et al. Metabolic syndrome: Risk factor distribution and 18-year mortality in the multiple risk factor intervention trial. *Diabetes Care* 2006; **29**: 123–130.
 22. Howard BV, Best LG, Galloway JM, Howard WJ, Jones K, Lee ET, et al. Coronary heart disease risk equivalence in diabetes depends on concomitant risk factors. *Diabetes Care* 2006; **29**: 391–397.
 23. Bots ML. Carotid intima-media thickness as a surrogate marker for cardiovascular disease in intervention studies. *Curr Med Res Opin* 2006; **22**: 2181–2190.
 24. Uekita K, Hasebe N, Funayama N, Aoyama H, Kuroda K, Aizawa H, et al. Cervical and intracranial atherosclerosis and silent brain infarction in Japanese patients with coronary artery disease. *Cerebrovasc Dis* 2003; **16**: 61–68.
 25. Mattace-Raso F, van Popele NM, Schalekamp MA, van der Cammen TJ. Intima-media thickness of the common carotid arteries is related to coronary atherosclerosis and left ventricular hypertrophy in older adults. *Angiology* 2002; **53**: 569–574.
 26. Sun K, Takasu J, Yamamoto R, Yokoyama K, Taguchi R, Itani Y, et al. Assessment of aortic atherosclerosis and carotid atherosclerosis in coronary artery disease. *Jpn Circ J* 2000; **64**: 745–749.
 27. Papamichael CM, Lekakis JP, Stamatiopoulos KS, Papaioannou TG, Alevizaki MK, Cimponeriu AT, et al. Ankle-brachial index as a predictor of the extent of coronary atherosclerosis and cardiovascular events in patients with coronary artery disease. *Am J Cardiol* 2000; **86**: 615–618.
 28. Igarashi Y, Chikamori T, Tomiyama H, Usui Y, Hida S, Tanaka H, et al. Diagnostic value of simultaneous brachial and ankle blood pressure measurements for the extent and severity of coronary artery disease as assessed by myocardial perfusion imaging. *Circ J* 2005; **69**: 237–242.
 29. Li J, Luo Y, Xu Y, Yang J, Zheng L, Hasimu B, et al. Risk factors of peripheral arterial disease and relationship between low ankle-brachial index and mortality from all-cause and cardiovascular disease in Chinese patients with type 2 diabetes. *Circ J* 2007; **71**: 377–381.
 30. Chang ST, Chen CL, Chu CM, Lin PC, Chung CM, Hsu JT, et al. Ankle–arm index is a useful test for clinical practice in outpatients with suspected coronary artery disease. *Circ J* 2006; **70**: 686–690.
 31. Imanishi R, Seto S, Toda G, Yoshida M, Ohtsuru A, Koide Y, et al. High brachial–ankle pulse wave velocity is an independent predictor of the presence of coronary artery disease in men. *Hypertens Res* 2004; **27**: 71–78.
 32. Park SM, Seo HS, Lim HE, Shin SH, Park CG, Oh DJ, et al. Assessment of arterial stiffness index as a clinical parameter for atherosclerotic coronary artery disease. *Circ J* 2005; **69**: 1218–1222.
 33. Resnick HE, Lindsay RS, McDermott MM, Devereux RB, Jones KL, Fabsitz RR, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: The Strong Heart Study. *Circulation* 2004; **109**: 733–739.
 34. Sukhija R, Aronow WS, Yalamanchili K, Peterson SJ, Frishman WH, Babu S. Association of ankle–brachial index with severity of angiographic coronary artery disease in patients with peripheral arterial disease and coronary artery disease. *Cardiology* 2005; **103**: 158–160.
 35. Su HM, Voon WC, Lin TH, Lee KT, Chu CS, Lee MY, et al. Ankle–brachial pressure index measured using an automated oscillometric method as a predictor of the severity of coronary atherosclerosis in patients with coronary artery disease. *Kaohsiung J Med Sci* 2004; **20**: 268–272.
 36. Faglia E, Manuela M, Antonella Q, Michela G, Vincenzo C, Maurizio C, et al. Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: An open-label randomized pilot study. *Am Heart J* 2005; **149**: e1–e6.
 37. Pepine CJ, Cohn PF, Deedwania PC, Gibson RS, Handberg E, Hill JA, et al. Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life: The Atenolol Silent Ischemia Study (ASIST). *Circulation* 1994; **90**: 762–768.
 38. Rogers WJ, Bourassa MG, Andrews TC, Bertolet BD, Blumenthal RS, Chaitman BR, et al. Asymptomatic Cardiac Ischemia Pilot (ACIP) study: Outcome at 1 year for patients with asymptomatic cardiac ischemia randomized to medical therapy or revascularization: The ACIP Investigators. *J Am Coll Cardiol* 1995; **26**: 594–605.
 39. Eagle KA, Guyton RA, Davidoff R, Ewy GA, Fonger J, Gardner TJ, et al. ACC/AHA guidelines for coronary artery bypass graft surgery: Executive summary and recommendations: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to revise the 1991 guidelines for coronary artery bypass graft surgery). *Circulation* 1999; **100**: 1464–1480.
 40. Erne P, Schoenenberger AW, Burckhardt D, Zuber M, Kiowski W, Buser PT, et al. Effects of percutaneous coronary interventions in silent ischemia after myocardial infarction: The SWISSI II randomized controlled trial. *JAMA* 2007; **297**: 1985–1991.