A Low Ankle Brachial Index is Associated with an Increased Risk of Cardiovascular Disease:The Hisayama Study

小嶋, 巌

https://doi.org/10.15017/2534521

出版情報：Kyushu University, 2019, 博士（医学）, 論文博士
バージョン：
権利関係：

Original Article

A Low Ankle Brachial Index is Associated with an Increased Risk of Cardiovascular Disease: The Hisayama Study

Iwao Kojima[1,2], Toshiharu Ninomiya[1,3], Jun Hata[1,3], Masayo Fukuhara[1,3], Yoichiro Hirakawa[1,3], Naoko Mukai[1,3], Daigo Yoshida[1], Takanari Kitazono[3] and Yutaka Kiyohara[1]

[1]Department of Environmental Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[2]Research and Development Department, Omron Healthcare, Co., Ltd., Kyoto, Japan
[3]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

***Aim*: Peripheral artery disease (PAD), defined as a decreased ankle brachial index (ABI), is a risk factor for cardiovascular disease; however, few studies have assessed the relationship between a low ABI and cardiovascular risks in Asian populations. We herein examined the relationship between the ABI and the development of cardiovascular disease in a Japanese community.**

***Methods*: A total of 2,954 community-dwelling Japanese individuals without prior cardiovascular disease ≥ 40 years of age were followed up for an average of 7.1 years. The subjects' ABIs were categorized into the three groups: low (≤ 0.90), borderline (0.91-0.99) and normal (1.00-1.40). We estimated the relationship between the ABI and cardiovascular risk using a Cox proportional hazards model.**

***Results*: During the follow-up period, 134 subjects experienced cardiovascular events. The incidence of cardiovascular disease across the ABI values was significantly different ($p<0.001$). After adjusting for confounding factors, namely age, sex, systolic blood pressure, use of anti-hypertensive drugs, diabetes, total cholesterol, high-density lipoprotein cholesterol, obesity, smoking, alcohol intake and regular exercise, individuals with a low ABI were at 2.40-fold (95% confidence interval [CI] 1.14-5.06) greater risk of cardiovascular disease and 4.13-fold (95% CI 1.62-10.55) greater risk of coronary heart disease.**

***Conclusions*: Our findings suggest that individuals with an ABI of ≤ 0.90 have an increased risk of cardiovascular events, independent from traditional risk factors, in the general Japanese population.**

J Atheroscler Thromb, 2014; 21:966-973.

Key words: Peripheral artery disease, Ankle brachial index, Cardiovascular disease, Prospective study, Epidemiology

Introduction

Peripheral artery disease (PAD) of the lower extremities is an atherosclerotic disease that can cause intermittent claudication, limb ischemia, gangrene, amputations and subsequent decrements in the patient's functional capacity and quality of life[1,2]. In addition, the presence of PAD is an indicator of systemic atherosclerosis in other vascular territories, such as the coronary, carotid and cerebrovascular arteries[3]. Some epidemiological evidence suggests that individuals with PAD are at an increased risk of cardiovascular mortality and morbidity, such as that involving coronary heart disease and brain infarction[4-9]. The manifestations of PAD are thus attended by significant personal, social and economic burdens, and PAD is increasingly being recognized as a health problem

Address for correspondence: Toshiharu Ninomiya, Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashiku, Fukuoka 812-8582, Japan
E-mail: nino@intmed2.med.kyushu-u.ac.jp
Received: November 19, 2013
Accepted for publication: March 10, 2014

worldwide.

Screening to identify individuals with asymptomatic PAD is important, not only for preventing complications directly related to PAD, but also inhibiting the development of cardiovascular disease (CVD). However, the findings of clinical examinations (e.g., skin color and temperature, peripheral pulse and bruits) have poor sensitivity for the detection of asymptomatic PAD[10]. The ankle brachial index (ABI), which is calculated as the ratio of the ankle systolic blood pressure (SBP) to the brachial SBP, is a simple, noninvasive and relatively cost-effective measurement for assessing individuals with asymptomatic PAD[11].

Several epidemiological studies have demonstrated that a lower ABI is associated with a higher cardiovascular risk[4-9]. Meta-analyses of population-based cohort studies conducted in Western countries have also suggested that individuals with an ABI below 0.90 have a significantly greater risk of coronary heart disease, stroke and cardiovascular death[12, 13]. Recent guidelines from the European Society of Cardiology, European Society of Hypertension, American College of Cardiology Foundation (ACC) and American Heart Association (AHA) recommend estimating the ABI to detect and manage asymptomatic PAD[14-16]. However, the relationship between the ABI and the incidence of CVD has not been fully addressed in general Asian populations. It is important to determine whether the cut-off values for the ABI used in epidemiological studies conducted in Western populations are applicable to Asian populations. We herein present the findings of a prospective cohort study that investigated the relationship between the ABI and the incidence of CVD in a general Japanese population.

Methods

Study Population

The Hisayama Study is an ongoing prospective cohort study for CVD and its risk factors in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan. The population of the town is approximately 8,000, and full community surveys of the residents have been repeated since 1961[17]. In 2002 and 2003, a screening survey for the present study was performed. The detailed description of this survey has been published previously[18]. Briefly, a total of 3,328 residents 40 years of age or older (77.6% of the total population of this age group) participated in the examination and underwent a comprehensive assessment. We excluded 30 subjects who did not consent to participate in the study, 190 subjects who had a medical history of CVD and 152 subjects with no data for the ABI. Two subjects with an ABI of >1.40 who were considered to have incompressible calcified arteries in the legs[19] were also excluded because the number of subjects was too small to perform a reliable risk estimation. Finally, the remaining 2,954 participants (1,262 men and 1,692 women) were enrolled.

Follow-Up

The subjects were followed up prospectively from the date of undergoing a comprehensive assessment until November 2009 using annual health examinations. The patient's health status was checked yearly by mail or telephone for any subjects who did not undergo the annual examination in a given year or who moved out of the town. A daily monitoring system was also established among the study team, local physicians and the staff of the health and welfare office in the town. When a subject died, an autopsy was performed at the Department of Pathology of Kyushu University.

ABI Measurement

The ABI was measured with the subject in the supine position after at least five minutes of rest using an automatic oscillometric apparatus (BP-203PRE II form PWV/ABI; Omron Healthcare, Kyoto, Japan). Four oscillometric cuffs were wrapped on both brachia and ankles. The cuffs were connected to a central unit that contained four pressure control pumps and four pressure sensors to automatically determine the blood pressure on the four limbs. The ABI was defined as the ankle SBP/brachial SBP ratio, for which the higher value of the brachial SBP between the right and left arms was used. Two readings of the ABI were measured as the same time on the right side and left side, and the lower value was used in the present study. We categorized the ABIs into three groups: low (≤ 0.90), borderline (0.91-0.99) and normal (1.00-1.40), according to the guidelines of the ACC Foundation and AHA[16].

Risk Factor Measurement

Self-administered questionnaires concerning the subject's current use of anti-hypertensive agents, insulin and oral glucose-lowering agents, as well as smoking habits and alcohol intake were checked by trained interviewers at the time of screening. These variables were classified as being either habitual or not. The subjects engaging in sports or other forms of exertion ≥ 3 times a week during their leisure time made up a regular exercise group. Blood pressure was measured three times using an automated sphygmomanometer

with the subject in the sitting position after at least five minutes of rest. The mean of three readings was used in this study. Hypertension was defined as a blood pressure of ≥ 140/90 mmHg and/or the current use of anti-hypertensive agents. The plasma glucose levels were measured according to the glucose oxidase method. Diabetes was defined as a fasting plasma glucose level of ≥ 7.0 mmol/L (126 mg/dL), two-hour post-loaded or casual glucose level of ≥ 11.1 mmol/L (200 mg/dL) and/or the current use of insulin or oral glucose-lowering agents. The serum total and high-density lipoprotein (HDL) cholesterol concentrations were determined enzymatically. Body height and weight were measured with the subject in light clothing without shoes, and the body mass index (BMI) was calculated as body weight/body height^2 (kg/m^2). Obesity was defined as a BMI of ≥ 25.0 kg/m^2. All clinical examinations and blood tests were conducted on the same day as the ABI measurements.

Definition of Cardiovascular Disease

The main outcomes of this study were first-ever events of CVD and its subtypes (coronary heart disease, ischemic stroke and hemorrhagic stroke). Coronary heart disease was defined as acute myocardial infarction, silent myocardial infarction, sudden cardiac death within one hour after the onset of acute illness or the use of coronary interventions (coronary artery bypass surgery and angioplasty). Acute myocardial infarction was diagnosed when a subject met at least two of the following criteria: (1) typical symptoms, including prolonged severe anterior chest pain, (2) abnormally high levels of cardiac enzymes confirmed more than twice, (3) evolving diagnostic electrocardiographic changes and (4) morphological changes, including local asynergy of the cardiac wall motion on electrocardiography, persistent perfusion defects on cardiac scintigraphy or myocardial necrosis and/or the presence of scars measuring 1 cm or longer accompanied by coronary atherosclerosis at autopsy.

Silent myocardial infarction was defined as myocardial scarring without any historical indication of clinical symptoms or abnormal changes in cardiac enzymes. Stroke was defined as the sudden onset of nonconvulsive and focal neurological deficits that continued for >24 hours and subclassified as either ischemic or hemorrhagic. All cardiovascular events were assessed based on the findings of a physical examination, review of all available clinical data, including medical records and brain imaging, and an autopsy by a panel of study members who remained blind to the information of the ABI values of the subjects.

Statistical Analysis

We analyzed the linear trends in the mean values and frequencies of the risk factors across the ABI groups using a linear regression analysis and logistic regression analysis, respectively. The event-free survival rates for CVD based on the ABI group were calculated according to the Kaplan-Meier method and compared using a log-rank test. We calculated the incidence of CVD using the person-year method. The hazard ratios (HRs) with 95% confidential intervals (CIs) of cardiovascular events according to the ABI were estimated using a Cox proportional hazards model. The SAS software package (SAS Institute, Cary, NC) was used to perform all statistical analyses. Two-sided p values of <0.05 were considered to be significant in all analyses.

Ethical Considerations

This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research. Written informed consent was obtained from all participants.

Results

The baseline characteristics of the study population according to the ABI are shown in **Table 1**. The prevalence of low, borderline and normal ABI values were 1.4% ($n=40$), 7.3% ($n=216$) and 91.3% ($n=2,698$), respectively. The subjects with a low ABI were significantly older than those with borderline or normal ABI values. The mean SBP and frequency of diabetes were significantly increased among the subjects with a low ABI.

During the average 7.1-year follow-up period, 134 subjects experienced cardiovascular events, including 85 stroke events and 54 coronary heart disease events. The event-free survival rates for CVD according to the ABI are shown in **Fig. 1A**. The cardiovascular event-free survival rates across the ABI values were significantly different (log-rank $p<0.001$). The subjects with a low ABI had a 5.41-fold (95% CI: 2.64-11.08) higher risk of cardiovascular events compared to those with a normal ABI, whereas there was no evidence of any differences between the subjects with borderline and normal ABI values ($p=0.51$) (**Table 2**). This relationship remained substantially unchanged after adjusting for age and sex (HR 2.90 [95% CI: 1.39-6.05]) as well as potential confounding factors, namely, age, sex, systolic blood pressure, anti-hypertensive agents, diabetes, serum total cholesterol, serum HDL cholesterol, obesity, smoking habits, alcohol intake and regular exercise (HR 2.40 [95% CI: 1.14-

Table 1. Baseline characteristics of the study population according to the ABI (ankle brachial index)

Variables	ABI level			*P* for trend
	Normal (1.00-1.40) *n* = 2,698	Borderline (0.91-0.99) *n* = 216	Low (≤ 0.90) *n* = 40	
Age, years	60 (11)	59 (14)	69 (14)	< 0.001
Male, %	43.4	34.7	42.5	0.07
Systolic blood pressure, mmHg	131.5 (20.3)	128.8 (24.1)	145.1 (27.9)	< 0.001
Diastolic blood pressure, mmHg	78.8 (11.6)	76.9 (13.4)	78.9 (16.2)	0.08
Anti-hypertensive agents, %	21.4	19.4	35.0	0.43
Hypertension, %	41.5	36.1	62.5	0.59
Diabetes, %	16.3	21.8	37.5	< 0.001
Serum total cholesterol, mmol/L	5.28 (0.91)	5.43 (0.97)	5.16 (0.86)	0.05
Serum HDL cholesterol, mmol/L	1.63 (0.42)	1.59 (0.42)	1.50 (0.39)	0.06
Body mass index, kg/m^2	23.2 (3.3)	23.1 (4.0)	22.3 (2.6)	0.19
Obesity, %	27.0	27.3	15.0	0.33
Alcohol intake, %	45.6	37.0	47.5	0.48
Smoking habit, %	22.9	22.2	17.5	0.11
Regular exercise, %	10.8	9.3	12.5	0.80

ABI, ankle brachial index; HDL, high-density lipoprotein.
The values are presented as the mean (standard deviation) or percentage.

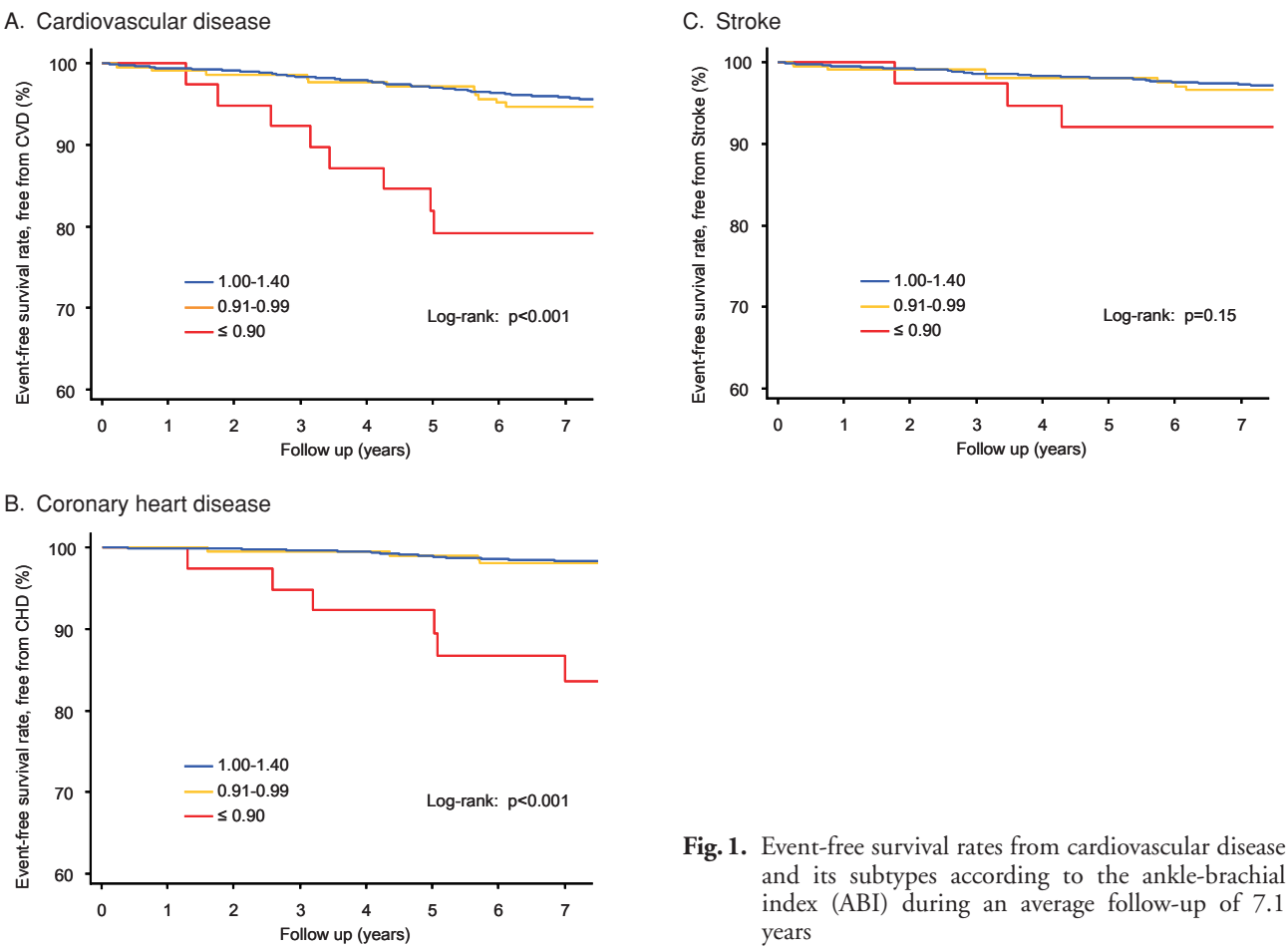

Fig. 1. Event-free survival rates from cardiovascular disease and its subtypes according to the ankle-brachial index (ABI) during an average follow-up of 7.1 years

Table 2. Relationships between ankle brachial index (ABI) and the development of cardiovascular disease, stroke and coronary heart disease during the 7.1-year average follow-up period

ABI level	Median of ABI	No. of events	Incidence[a] (/10³ PYs)	Unadjusted			Age- and sex-adjusted			Multivariable-adjusted[b]		
				HR (95%CI)	*p*	*p* for trend	HR (95%CI)	*p*	*p* for trend	HR (95%CI)	*p*	*p* for trend
Cardiovascular disease												
Normal (1.00-1.40)	1.10	115	6.1	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Borderline (0.91-0.99)	0.97	11	7.6	1.23 (0.66-2.29)	0.51	<0.001	1.27 (0.68-2.36)	0.45	0.009	1.09 (0.58-2.05)	0.78	0.054
Low (≤ 0.90)	0.81	8	32.8	5.41 (2.64-11.08)	<0.001		2.90 (1.39-6.05)	0.005		2.40 (1.14-5.06)	0.02	
Coronary heart disease												
Normal (1.00-1.40)	1.10	44	2.3	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Borderline (0.91-0.99)	0.97	4	2.7	1.17 (0.42-3.24)	0.77	<0.001	1.24 (0.45-3.47)	0.68	0.001	0.95 (0.34-2.70)	0.93	0.018
Low (≤ 0.90)	081	6	23.7	10.50 (4.47-24.64)	<0.001		5.34 (2.20-12.97)	<0.001		4.13 (1.62-10.55)	0.003	
Stroke												
Normal (1.00-1.40)	1.10	75	4.0	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Borderline (0.91-0.99)	0.97	7	4.7	1.21 (0.56-2.62)	0.63	0.12	1.23 (0.57-2.67)	0.60	0.37	1.11 (0.50-2.42)	0.80	0.68
Low (≤ 0.90)	0.81	3	11.8	2.96 (0.93-9.38)	0.07		1.60 (0.49-5.16)	0.43		1.23 (0.38-4.02)	0.73	
Ischemic stroke												
Normal (1.00-1.40)	1.10	46	2.4	1.00 (reference)			1.00 (reference)			1.00 (reference)		
Borderline (0.91-0.99)	0.97	6	4.0	1.69 (0.72-3.97)	0.22	0.33	1.70 (0.73-3.99)	0.22	0.07	1.48 (0.62-3.51)	0.38	0.16
Low (≤ 0.90)	0.81	3	11.8	4.84 (1.50-15.55)	0.008		2.48 (0.75-8.23)	0.14		2.07 (0.62-6.93)	0.24	
Hemorrhagic stroke												
Normal (1.00-1.40)	1.10	29	1.52	1.00 (reference)			1.00 (reference)			NA		
Borderline (0.91-0.99)	0.97	1	0.58[c]	0.38(0.05-2.77)	0.34[c]	NA	0.35 (0.05-2.60)	0.31[c]	NA			
Low (≤ 0.90)	0.81	0								NA		

PYs, person-years; HR, hazard ratio; CI, confidence interval; NA, not analyzed.
[a]Values were unadjusted.
[b]The risk estimates were adjusted for age, sex, systolic blood pressure, anti-hypertensive agents, diabetes, serum total cholesterol, serum high-density lipoprotein cholesterol, obesity, smoking habits, alcohol intake and regular exercise.
[c]The borderline and low groups were combined.

5.06]).

With regard to the subtype of CVD, the event-free survival rate for coronary heart disease was significantly different across the ABI groups (log-rank $p<0.001$), whereas that for stroke was not (log-rank $p=0.15$) (**Fig. 1B**, **C**). The multivariable-adjusted risk of coronary heart disease was significantly increased (by 4.13-fold; 95% CI: 1.62-10.55) in the subjects with a low ABI compared to that observed in the subjects with a normal ABI, while there was no evidence of a significant relationship between the ABI values and the risk of stroke. Among the stroke subtypes, however, the univariate analysis revealed that those with a low ABI were at an increased risk of ischemic stroke (HR 4.84; 95% CI: 1.50-15.55), although the significance of the relationship disappeared after adjusting for the above-mentioned confounding factors. No clear relationships between the ABI values and hemorrhagic stroke were observed when the borderline and low ABI groups were combined, as the number of events was zero in the low ABI group.

Discussion

The present results clearly demonstrated that an ABI of 0.90 or lower is significantly associated with an increased risk of cardiovascular events. This relationship remained significant after adjusting for potential confounding factors. To the best of our knowledge, this is the first study to prospectively investigate the relationship between the ABI and cardiovascular events in a community-based cohort study of a general Asian population.

The ABI has been investigated as a risk factor in several population-based cohort studies, primarily in North America and Europe[4-8]. Almost all of these studies found that an ABI of ≤ 0.90 is significantly associated with an increased risk of total mortality[4-6], cardiovascular mortality[4-6] and incident coronary heart disease[4, 7]. The ABI Collaboration, an individ-

ual-based meta-analysis of 16 community-dwelling cohorts conducted in Western countries, clearly demonstrated that a lower ABI (≤ 0.90) approximately doubles the risk of total mortality, cardiovascular mortality and major coronary events compared to an ABI of 1.11-1.20, independent of the Framingham risk score[13].

With regard to Asian populations, a significant relationship between the ABI and cardiovascular risks has been found in several hospital-based prospective studies conducted among patients with risk factors such as metabolic syndrome, ischemic heart disease and chronic kidney disease[20-22]. For example, the China ABI Cohort Study, a hospital-based study of 3,210 Chinese patients with two or more cardiovascular risk factors, showed that the multivariable-adjusted risk of cardiovascular mortality increased significantly (by 2.0 times) in the subjects with an ABI below 0.90 compared to that observed in the subjects with an ABI above 0.90[20]. However, limited studies have addressed this issue in the general Asian population. Our findings suggest that an ABI of ≤ 0.90 is an independent risk factor for the incidence of CVD in a community-based Asian population.

In the ABI Collaboration[13], subjects with an ABI from 0.91 to 1.10 and those with a high ABI (> 1.40), which may be related to poor arterial compressibility resulting from stiffness and calcification, were at slightly increased absolute risks of total mortality, cardiovascular mortality and major coronary events. These results suggest that subjects with an ABI of 0.91 to 1.10 or greater than 1.40 may have slightly higher risks of these outcomes than those with a normal ABI, although the widely accepted high-risk cut-off value of 0.90 is reasonable[11]. Based on these findings, the ACC/AHA practice guidelines define ABI categories as low ABI (severe and mild to moderate), borderline ABI, normal ABI and high ABI[16]. In the present study, however, we did not find that borderline ABI was related to the risk of cardiovascular events, likely due to the limited statistical power. Likewise, we were unable to address the relationship between an ABI of >1.40 and cardiovascular risk, because only two subjects had an ABI of >1.40. The relationship between a borderline or high ABI and the risk of cardiovascular events should be addressed in large samples of Asian populations.

When we investigated the subtypes of cardiovascular events, we observed that, after adjusting for confounding factors, a low ABI was significantly related to an increased risk of coronary heart disease events, but not the risk of stroke. Several epidemiological studies conducted in Western countries have shown a low ABI to be a significant risk factor for stroke events[5, 19, 23]. The Atherosclerosis Risk in Communities Study also found that a low ABI is associated with a higher incidence of ischemic stroke after adjusting for age, race, sex and center; however, this significant relationship disappeared after adjusting for other confounding factors[8]. These results are similar to the present findings, although the relationship in the present study did not reach a level of statistical significance and was largely attenuated compared to that observed in previous studies, possibly because lacunar stroke is the dominant type of ischemic stroke in Japan, whereas large-artery atherothrombotic brain infarction is more prevalent in Western countries[24]. Given the etiology of each stroke subtype, the risk of atherothrombotic brain infarction, as well as coronary heart disease, may be expected to increase in subjects with a low ABI because PAD is an atherosclerotic disease of the large arteries. Atherosclerotic changes in cerebral arteries, as well as coronary arteries, may already be advanced among subjects with PAD defined as an ABI of ≤ 0.9, as PAD is attributable to atherosclerotic remodeling of lower extremity peripheral arteries. The risk of atherothrombotic brain infraction may thus be expected to increase in subjects with a low ABI. Large-scale studies are therefore required to elucidate the relationship between a low ABI and the risk of stroke subtypes.

Several limitations of the present study should be noted. First, the generalizability of our findings may be limited, as 152 subjects without available ABI data were excluded from the study. Compared to the subjects who were included, the excluded subjects were older (mean age: 81 years for the excluded subjects vs. 60 years for the included subjects) and more likely to have hypertension (73.7% vs. 43.0%) or a history of cardiovascular events (21.5% vs. 4.5%). This bias would lead to underestimation of the relationship between the ABI and cardiovascular risks. Second, only a single ABI measurement was obtained at the baseline examination. This may have caused the misclassification of subjects into the wrong ABI group. Such misclassification, if present, would weaken the relationship found in this study, biasing the results toward the null hypothesis. Third, we were unable to obtain information regarding the subjects' medical treatment during the follow-up period. The lack of this information may have reduced the accuracy of our findings to some extent. In addition, we used an automatic device to measure blood pressure in the four limbs and the oscillometric method instead of the standard doppler method. The standard doppler method is recommended in the ACC/AHA guidelines

because some devices using oscillometric blood pressure have been found to overestimate the actual ankle blood pressure, especially in subjects with a very low ankle blood pressure[25]. However, the precision of our device has been validated in both Japanese and European populations[26, 27], and thus, although this limitation may have reduced the precision of the ABI values to some extent, it is unlikely to have altered the findings substantially.

In conclusion, the present findings indicate that, in a general Japanese population, the subjects with an ABI of ≤ 0.90 had an increased risk of cardiovascular events, independent of traditional cardiovascular risk factors. Because the ABI is a noninvasive and user-friendly method for estimating the extent of systemic atherosclerotic disease, it may be applied more broadly in general practice to identify individuals at a high risk of developing CVD.

Acknowledgments

We thank the staff of the Division of Health and Welfare of Hisayama for their cooperation in this study.

Disclosures

I. Kojima is a former employee of Omron Healthcare Co., Ltd. There are no other conflicts of interest to declare.

Conflicts of Interest

The first author, Iwao Kojima is a former employee for Omron Healthcare, Co., Ltd., which produces the device used to measure the ABI. All remaining authors report no conflicts of interest.

Grant Support

This study was supported in part by Grants-in-Aid for Scientific Research on Innovative Areas (22116010) and Scientific Research (A) (25253048) from the Ministry of Education, Culture, Sports, Science and Technology of Japan and Health and Labour Sciences Research Grants from the Ministry of Health, Labour and Welfare of Japan (Comprehensive Research on Life-Style Related Diseases including Cardiovascular Diseases and Diabetes Mellitus: H22-Junkankitou [Seishuu]-Ippan-005, H23- Junkankitou [Seishuu]-Ippan-005, H25- Junkankitou [Seishuu]-Ippan-005 and H25- Junkankitou [Seishuu]-Sitei-022; and Comprehensive Research on Dementia: H25-Nichisho-Ippan-004).

References

1) Dumville JC, Lee AJ, Smith FB, Fowkes FG: The health-related quality of life of people with peripheral arterial disease in the community: the Edinburgh Artery Study. Gen Pract, 2004; 54: 826-831
2) Yan BP, Moran D, Hynes BG, Kiernan TJ, Yu CM: Advances in endovascular treatment of critical limb ischemia. Circ J, 2011; 75: 756-765
3) Ikeda N, Kogame N, Iijima R, Nakamura M, Sugi K: Impact of carotid artery ultrasound and ankle-brachial index on prediction of severity of SYNTAX score. Circ J, 2013; 77: 712-716
4) Ogren M, Hedblad B, Isacsson SO, Janzon L, Jungquist G, Lindell SE: Non-invasively detected carotid stenosis and ischaemic heart disease in men with leg arteriosclerosis. Lancet, 1993; 342: 1138-1141
5) Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV: Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. BMJ, 1996; 313: 1440-1444
6) Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF, Powe NR, Siscovick D: Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. Arterioscler Thromb Vasc Biol, 1999; 19: 538-545
7) Weatherley BD, Nelson JJ, Heiss G, et al.: The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-2001. BMC Cardiovasc Disord, 2007; 7: 3
8) Tsai AW, Folsom AR, Rosamond WD, Jones DW: Ankle-brachial index and 7-year ischemic stroke incidence: the ARIC Study. Stroke, 2001; 32: 1721-1724
9) Abbott RD, Rodriguez BL, Petrovitch H, Yano K, Schatz IJ, Popper JS, Masaki KH, Ross GW, Curb JD: Ankle-brachial blood pressure in elderly men and the risk of stroke: the Honolulu Heart Program. J Clin Epidemiol, 2001; 54: 973-978
10) Khan NA, Rahim SA, Anand SS, Simel DL, Panju A: Does the clinical examination predict lower extremity peripheral arterial disease? JAMA, 2006; 295: 536-546
11) Hirsh AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al.: ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): Circulation, 2006; 113: e463-e654
12) Doobay AV, Anand SS: Sensitivity and specificity of the

ankle-brachial index to predict future cardiovascular outcomes: a systematic review. Arterioscler Thromb Vasc Biol, 2005; 25: 1463-1469
13) Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al.: Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. JAMA, 2008; 300: 197-208
14) Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clément D, Collet JP, et al.: ESC Guidelines on the diagnosis and treatment of peripheral artery diseases: Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J, 2011; 32: 2851-2906
15) Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M et al.: 2013 ESH/ESC Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens, 2013; 31: 1281-1357
16) Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, et al.: 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol, 2011; 58: 2020-2045
17) Ohmura T, Ueda K, Kiyohara Y, Kato I, Iwamoto H, Nakayama K, et al.: Prevalence of type 2 (non-insulin-dependent) diabetes mellitus and impaired glucose tolerance in the Japanese general population: the Hisayama Study. Diabetologia, 1993; 36: 1198-1203
18) Ninomiya T, Kojima I, Doi Y, Fukuhara M, Hirakawa Y, Hata J, et al.: Brachial-ankle pulse wave velocity predicts the development of cardiovascular disease in a general Japanese population: the Hisayama Study. J Hypertens, 2013; 31: 477-483
19) Sutton-Tyrrell K, Venkitachalam L, Kanaya AM, Boudreau R, Harris T, Thompson, et al.: Relationship of ankle blood pressures to cardiovascular events in older adults. Stroke, 2008; 39: 863-869
20) Li X, Luo Y, Xu Y, Li J, Hu D: Relationship of ankle-brachial index with all-cause mortality and cardiovascular mortality after a 3-year follow-up: the China ankle-brachial index cohort study. J Hum Hypertens, 2010; 24: 111-116
21) Cang Y, Li J, Li YM, Zhou Y, Wu YZ, Li XK, et al.: Relationship of a low ankle-brachial index with all-cause mortality and cardiovascular mortality in Chinese patients with metabolic syndrome after a 6-year follow-up: a Chinese prospective cohort study. Intern Med, 2012; 51: 2847-2856
22) Zheng L, Li J, Hu D, Luo Y, Li X, Xu Y, Sun Z, Sun Y: Association of low ankle-brachial index with mortality in patients with ischemic heart disease. J Atheroscler Thromb, 2010; 17: 759-767
23) Meves SH, Diehm C, Berger K, Pittrow D, Trampisch HJ, Burghaus I, et al.: Peripheral arterial disease as an independent predictor for excess stroke morbidity and mortality in primary-care patients: 5-year results of the getABI study. Cerebrovasc Dis, 2010; 29: 546-554
24) Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y, et al.: Cardiovascular disease and risk factors in Asia: a selected review. Circulation, 2008; 118: 2702-2709
25) Aboyans V, Criqui MH, Abraham P, Allison MA, Creager MA, Diehm C, et al.: Measurement and interpretation of the ankle-brachial index: a scientific statement from the American Heart Association. Circulation, 2012; 126: 2890-2909
26) 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. Cardiology, 2004; 94: 868-872
27) Richart T, Kuznetsova T, Wizner B, Struijker-Boudier HA, Staessen JA: Validation of automated oscillometric versus manual measurement of the ankle-brachial index. Hypertens Res, 2009; 32: 884-888