Original Article

Relationship between the Ankle-Brachial Index and the Risk of Coronary Heart Disease and Stroke: The Circulatory Risk in Communities Study

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Aim: **Patients with peripheral artery disease (PAD) are at a high risk of cardiovascular disease (CVD) among Western populations. However, evidence for an elevated risk in Asian populations is limited.**
Methods: **This prospective cohort study examined 939 Japanese men 60-74 years of age at the time of the baseline survey. A total of 115 cases of CVD were detected during a median 9.3 years of follow-up, and the ankle brachial blood pressure index (ABI) functioned as a surrogate measurement of PAD.**
Results: **The age-adjusted risks of coronary heart disease, ischemic stroke and ischemic CVD (coronary heart disease and ischemic stroke) were higher among men in the lowest ABI tertile compared with that observed in the men in the highest tertile (<1.08 vs. >1.17). These associations did not change substantially after adjusting for cardiovascular risk factors. The respective multivariable hazard ratios (HRs, 95% CI) for the three conditions were as follows: 2.48 (1.08-5.71), *p* for trend= 0.03; 1.95 (0.94-4.02), *p* for trend=0.04; and 2.16 (1.25-3.72), *p* for trend=0.004. These results did not vary based on a comparison of the three ABI categories: ≤0.90, 0.91-1.10 and >1.10. The multivariable HRs (95% CI) for an ABI ≤0.90 versus >1.10 were as follows: 2.04 (0.67-6.20), *p* for trend=0.14 for coronary heart disease; 3.39 (1.10-10.5), *p* for trend=0.006 for ischemic stroke; and 2.61 (1.19-5.76), *p* for trend=0.003 for ischemic CVD. There were no associations between the ABI and the risk of hemorrhagic stroke.**
Conclusions: **A low ABI is associated with the risk of coronary heart disease, ischemic stroke and ischemic CVD in elderly Japanese men.**

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Key words: Ankle brachial index, Ischemic CVD, Follow-up studies

Introduction

Several epidemiological studies have reported that patients with peripheral artery disease (PAD) are at a high risk of cardiovascular disease (CVD)[1-3]. The ankle-brachial blood pressure index (ABI) allows for the estimation of the risk of CVD, with many prospective studies indicating an ABI of ≤0.90 to be associated with an increased risk of coronary heart disease[1, 4] and stroke[1, 5, 6] in Western countries. Additionally, a meta-analysis of 16 population cohort studies demonstrated that a low ABI (≤0.90) is associated with both CVD and total mortality[7].

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However, such evidence is limited in Asian populations. In one study, Chinese patients with metabolic syndrome and an ABI of ≤0.9 demonstrated an approximately two-fold higher risk of CVD-related mortality at the six-year follow-up visit[8]. Additionally, the Honolulu Heart Program reported that Japanese-American men with an ABI of <0.8 had an approximately three-fold higher risk of coronary heart disease during a three- to six-year follow-up period[9]. Furthermore, a recent systematic review of 34 community-based studies reported that the prevalence of an ABI of ≤0.90 increased by 23.5% from 2000 to 2010 among both men and women ≥25 years of age[10].

No previous prospective cohort studies have examined the relationship between a low ABI and the risk of coronary heart disease and stroke subtypes in Asian populations, although we previously evaluated the ABI with respect to various risk factors of CVD[2]. The aim of the present study was to determine the association between the ABI and the risk of coronary heart disease and stroke subtypes in the general Japanese population.

Methods

Study Population

The circulatory risk in communities study (CIRCS) is a dynamic community-based cohort study of five communities in Japan[11] involving an annual cardiovascular risk survey conducted since 1963. In the present study, the subjects consisted of 977 men 60-74 years of age who underwent measurement of the ABI between 1999 and 2000 in two rural communities of Ikawa town in northeast Japan ($n=343$) and Kyowa town in central Japan ($n=634$) among a total of 1,161 men (363 and 798, respectively) included in the risk factor survey. We excluded 32 men with a history of PAD and CVD at the baseline survey and six men with an ABI of >1.50, as an extremely high ABI normally reflects arterial rigidity, thereby preventing arterial compression[3]. Therefore, we ultimately analyzed data for 939 participants.

Research teams from the Osaka Center for Cancer and CVD Prevention, Osaka University and the University of Tsukuba have conducted annual cardiovascular risk surveys within the CIRCS in Ikawa since 1963 and Kyowa since 1981. The Ethics Committee of Osaka university approved the present study.

Measurement of the ABI and Cardiovascular Risk Factors

Trained technicians measured the ABI using a standard protocol described in a previous study[2, 12]. In 1999, systolic blood pressure was measured at the right brachial artery using a standard sphygmomanometer and at the right and left posterior tibial arteries using a bi-directional Doppler ES-100V II (Hayashi Denki Co., Japan). Standard 12-cm blood pressure cuffs were applied to both ankles and an appropriately sized cuff was applied to the right arm. After five minutes of rest, with the subject in the supine position, systolic blood pressure was measured in the right arm and both ankles, with a repeated measurements obtained 30 seconds later. The cuff was inflated rapidly to 20 mmHg above the palpated systolic blood pressure and then deflated at a rate of 2 mmHg per pulse. The first Korotkoff sound was recorded as the systolic pressure. In 2000, the ABI was measured using a FORM PWV/ABI device (Colin Co., Japan) in which an automatic sphygmomanometer with standard 12-cm blood pressure cuffs was applied to both ankles and one arm in order to calculate the ABI automatically. There were no differences between the ABI values obtained according to the two techniques ($n=36$): the mean (±SD) ABI measured with the manual and automatic systems was 1.07±0.17 and 1.08±0.18, respectively ($p=0.81$; Pearson correlation coefficient=0.82). Therefore, we combined the data for the ABI values measured in both 1999 and 2000 for the analysis[2]. An ABI of ≤0.90 in either leg was defined as a low ABI.

The present study used previously reported protocols for the following procedures: assessments of cardiovascular risk factors, such as height, weight, blood pressure, serum glucose, total and HDL-cholesterol levels, smoking status, drinking habits and use of medications for hypertension and diabetes mellitus; history-taking for PAD and CVD based on interviews; and quality control procedures[2, 12]. A systolic blood pressure of ≥140 mmHg diastolic blood pressure of ≥90 mmHg and/or the use of antihypertensive medications indicated hypertension. A fasting glucose level of ≥7.0 mmol/L, non-fasting glucose level of ≥11.1 mmol/L or the use of medications for diabetes mellitus indicated diabetes mellitus. Subjects who smoked ≥1 cigarette per day were defined as current smokers, with those who had smoked previously, but not for the past three months or more, defined as former smokers. An interviewer assessed the average weekly intake of alcohol in units of “go,” a traditional Japanese unit of volume corresponding to 23 g of ethanol, and converted the measurements to grams of ethanol per day.

Blood was withdrawn into plain, siliconized glass tubes, and the serum was separated for measurement of serum lipids and glucose. The fasting status at the time of blood collection was recorded, with fasting defined as a period of more than eight hours after the last meal (48.7% of the subjects). An automatic analyzer (Hitachi 7250, Hitachi Medical Corp., Ibaraki, Japan) was used to measure the total and HDL-cholesterol levels according to enzymatic methods at the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network (CRMLN)[13]. The same instrument was applied to measure the serum glucose level according to the hexokinase method.

Surveillance of CVD

The details of the protocol used to diagnose stroke and coronary heart disease have been described previously[11, 14]. Patients susceptible to stroke and/or coronary heart disease were identified based on national insurance claims, ambulance records, death certificates and reports by local physicians, public health nurses and volunteers. In order to confirm the diagnosis, we called, visited or invited the susceptible subjects to participate in the annual cardiovascular risk survey to obtain their clinical history. In cases of death, we obtained the subject's history from family members and medical records. In addition, physician epidemiologists reviewed the participants medical records held at local clinics and hospitals.

We diagnosed stroke according to the National Survey of Stroke criteria[15], which require a constellation of neurological deficits of sudden or rapid onset lasting ≥24 hours or until death. The presence of stroke and the subtype of ischemic or hemorrhagic stroke were determined on computed tomography (CT) and/or magnetic resonance imaging (MRI) using standardized criteria[16]. CT was used to confirm more than 90% of cases of stroke in the present study.

In addition, we applied modified coronary heart disease criteria proposed by the World Health Organization Expert Committee[17] and defined coronary heart disease as including myocardial infarction, angina pectoris and sudden cardiac death. Definitive myocardial infarction was defined as typical chest pain lasting for at least 30 minutes, accompanied by either the appearance of new abnormal persistent Q or QS waves or consistent changes in the cardiac enzyme levels or both. Typical chest pain for which there was no electrocardiographic evidence or findings related to the enzyme activity was defined as probable myocardial infarction. The definition of angina pectoris comprised repeated episodes of chest pain during effort, especially when walking, that usually disappeared rapidly following the cessation of effort or the use of sublingual nitroglycerin. The definition of sudden cardiac death included death within one hour of onset, witnessed cardiac arrest or abrupt collapse not preceded by symptoms lasting more than one hour[14]. Total CVD included total stroke and coronary heart disease, and ischemic CVD comprised ischemic stroke and coronary heart disease.

Statistical Analysis

The total number of years of follow-up for each subject was calculated from the year of the baseline survey to the first endpoint, including death, emigration or the end of the year 2009. Using an analysis of covariance, age-adjusted means and the prevalence of cardiovascular risk factors were calculated according to the ABI tertile: low (0.54-1.07), middle (1.08-1.17), high (1.18-1.47) or three categories of ABI values: ≤0.90, 0.91-1.10 and >1.10. The hazard ratios (HR) and 95% confidence intervals (95% CIs) for the incidence of CVD were calculated using the Cox proportional hazards model between the subjects in the highest ABI tertile (ABI >1.17) and the ABI >1.10 category.

The analyses of ischemic CVD were repeated with stratification according to established risk factors, such as the smoking status (never smokers vs. former or current smokers) and presence of hypertension or diabetes mellitus (yes vs. no). The significance of the interactions between the variables of smoking, hypertension and diabetes was tested using cross-product terms, with ABI categories in the multivariable models.

Potential confounding factors included: age (years), BMI (kg/m^2), systolic blood pressure (mmHg), serum total and HDL-cholesterol levels (mmol/L), smoking status (yes or no), ethanol intake (g/day), use of medications for hypertension (yes or no), history of diabetes mellitus (yes or no) and community. The SAS statistical package, version 9.3 (SAS Institute Inc., Cary, CA), was used for all analyses, and all *p* values for the statistical tests were two-tailed, with a *p* value of <0.05 being considered statistically significant.

Results

Table 1 shows the baseline characteristics of the patients according to the ABI tertile. The subjects in the lowest ABI tertile were older, smoked more frequently and had a lower mean BMI than those in the highest ABI tertile. There were no differences in characteristics across the ABI tertiles with regard to the mean systolic and diastolic blood pressure, total and HDL-cholesterol levels, ethanol intake and prevalence

Table 1. Age-adjusted means ± standard deviations and rates of selected cardiovascular risk factors according to the ABI tertile

	Tertiles of ABI			p for trend
	Low 0.54-1.07	Middle 1.08-1.17	High 1.18-1.47	
Number	314	313	312	
Age (year)	68.1 ± 4.2‡	67.1 ± 4.3	66.9 ± 4.1	< 0.001
Body mass index (kg/m^2)	22.7 ± 3.1‡	23.5 ± 2.8†	24.3 ± 3.0	< 0.001
Systolic blood pressure (mmHg)	139.2 ± 17.0	138.7 ± 17.1	140.2 ± 17.7	0.78
Diastolic blood pressure (mmHg)	81.2 ± 10.2	81.1 ± 10.8	81.7 ± 10.6	0.61
Total cholesterol (mmol/L)	5.06 ± 0.82	5.04 ± 0.93	5.09 ± 0.86	0.66
HDL-cholesterol (mmol/L)	1.48 ± 0.41	1.45 ± 0.38	1.48 ± 0.44	0.42
Alcohol intake (g/day)	23.9 ± 24.9	26.3 ± 26.0	25.0 ± 23.8	0.36
Current smokers (%)	45*	44*	36	0.12
Use of antihypertensive medication (%)	36	35	35	0.38
Diabetes mellitus (%)	11	11	12	0.50

*p < 0.05, †p < 0.01, ‡p < 0.01 compared with the ABI > 1.17 category.

of a history of hypertension and diabetes mellitus.

During a median follow-up of 9.3 years, this study documented 115 cases of total CVD, 69 cases of stroke (44 patients with ischemic stroke, 19 patients with hemorrhagic stroke and six patients with unclassified stroke), 46 cases of coronary heart disease (32 patients with myocardial infarction and 14 patients with angina pectoris) and 90 cases of ischemic CVD.

The age-adjusted risks of coronary heart disease, ischemic stroke, ischemic CVD and total CVD were higher among the subjects in the lowest ABI tertile than in those in the highest tertile (**Table 2**). These associations did not change substantially after adjusting for systolic blood pressure and other cardiovascular risk factors. The multivariable HRs (95% CI) were as follows: 2.48 (1.08-5.71), p for trend = 0.03 for coronary heart disease; 1.95 (0.94-4.02), p for trend = 0.04 for ischemic stroke; 2.16 (1.25-3.72), p for trend = 0.004 for ischemic CVD; and 1.70 (1.08-5.71), p for trend = 0.03 for total CVD. No excess or reduced risk was observed for any outcome associated with the middle ABI tertile compared with the lowest tertile. We did not use an ABI of > 1.30 or > 1.40 as a cut-off for a high ABI level, as there was only one case of ischemic stroke associated with a ABI value above this level. In addition, there were no associations between the ABI and the risk of hemorrhagic stroke.

The results did not differ substantially when comparing the three categories of ABI: ≤ 0.90, 0.91-1.10 and > 1.10. The men with an ABI of ≤ 0.90 had a higher risk of coronary heart disease, ischemic stroke, ischemic CVD and total CVD than those with an ABI of > 1.10, although the association for coronary heart disease did not reach statistical significance. The respective HRs for the four conditions were as follows: 2.04 (0.67-6.20), p for trend = 0.14; 3.39 (1.10-10.5), p for trend = 0.006; 2.61 (1.19-5.76), p for trend = 0.003; and 1.89 (0.88-4.06), p for trend = 0.03 (not shown in Table). When we excluded 51 subjects with an ABI of > 1.3 from the analysis, the respective HRs were as follows: 1.85 (0.61-5.61), p for trend = 0.21; 3.43 (1.11-10.6), p for trend = 0.009; 2.50 (1.13-5.53), p for trend = 0.006; and 1.82 (0.84-3.91), p for trend = 0.05 (data not shown in the Table).

Table 3 shows the HRs (95% CI) for ischemic CVD based on the ABI tertile, with stratification according to the smoking, hypertension and diabetes mellitus status. The association between the ABI and the risk of ischemic CVD was more evident in smokers, hypertensives and diabetics, although no significant interactions were observed between the risk factors and the incidence of ischemic CVD.

Discussion

In this study of Japanese men 60-74 years of age, the subjects in the lowest ABI tertile displayed an approximately two-fold higher risk of coronary heart disease and ischemic stroke than those in the highest tertile over a median follow-up period of 9.3 years. A comparison of the ABI categories of ≤ 0.90 and ≥ 1.10 showed a similar trend. The results for coronary heart disease are consistent with the findings of previous research in American[1, 4] and European subjects[5], including multivariable HRs for coronary heart disease of 1.41 (1.11-1.91) for subjects with an ABI of

Table 2. Age- and multivariable-adjusted hazard ratios for cardiovascular disease according to the ABI tertile

	Tertiles of ABI			p for trend	1-SD reduction of ABI**
	Low 0.54-1.07	Middle 1.08-1.17	High 1.18-1.47		
Person years	2,867	2,930	2,943		
Number	314	313	312		
Total stroke	32	15	22		
Age-adjusted HR	1.36 (0.78-2.35)	0.66 (0.34-1.28)	1.00	0.23	1.14 (0.92-1.40)
Multivariable HR	1.43 (0.81-1.33)	0.68 (0.35-1.33)	1.00	0.19	1.15 (0.93-1.43)
Ischemic stroke	24	8	12		
Age-adjusted HR	1.82 (0.91-3.66)	0.65 (0.27-1.60)	1.00	0.06	1.32 (1.04-1.68)*
Multivariable HR	1.95 (0.94-4.02)	0.69 (0.28-1.70)	1.00	0.04	1.36 (1.06-1.75)*
Hemorrhagic stroke	5	7	7		
Age-adjusted HR	0.73 (0.23-2.33)	0.99 (0.35-2.84)	1.00	0.60	0.79 (0.50-1.23)
Multivariable HR	0.76 (0.23-2.49)	1.02 (0.35-2.96)	1.00	0.64	0.81 (0.52-1.27)
Coronary heart disease	22	16	8		
Age-adjusted HR	2.63 (1.17-5.95)*	2.01 (0.86-4.70)	1.00	0.02	1.34 (1.06-1.69)*
Multivariable HR	2.48 (1.08-5.71)*	1.97 (0.84-4.64)	1.00	0.03	1.29 (1.02-1.64)*
Ischemic cardiovascular disease	46	24	20		
Age-adjusted HR	2.15 (1.26-3.65)†	1.19 (0.66-2.16)	1.00	0.003	1.33 (1.12-1.57)‡
Multivariable HR	2.16 (1.25-3.72)†	1.21 (0.66-2.20)	1.00	0.004	1.32 (1.11-1.57)†
Total cardiovascular disease	54	31	30		
Age-adjusted HR	1.70 (1.08-2.67)*	1.02 (0.62-1.68)	1.00	0.02	1.22 (1.04-1.42)*
Multivariable HR	1.70 (1.07-2.71)*	1.03 (0.62-1.71)	1.00	0.02	1.21 (1.03-1.42)*

*$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ compared with the ABI > 1.17 category or a 1-SD reduction in ABI. Multivariable adjustment for age (year), body mass index (kg/m^2), smoking and alcohol intake, total and HDL cholesterol levels (mmol/L), systolic blood pressure (mmHg), diabetes mellitus (yes) and use of medications for hypertension.
**1-SD of ABI = 0.11.

≤0.90 compared with an ABI of 0.91 to 1.30 among 2,886 white and black men and women 70-79 years of age[1)], 2.81 (1.77-4.45) for men with an ABI of < 0.90 compared with an ABI ≥ 0.90 among 12,186 white men and women 45-64 years of age[4)] and 1.89 (1.03-3.46) for subjects with an ABI of ≤ 0.90 compared with an ABI of > 0.90 among 1,592 white men and women 55-74 years of age[5)].

The finding that men with an ABI of ≤ 0.90 have a higher risk of ischemic stroke is supported by previous research in both American and European subjects[1, 5, 6)]. For example, the Edinburgh Artery Study reported that an ABI of ≤ 0.90 is associated with an increased risk of total stroke compared with an ABI of > 0.90, with a multivariable HR of 1.98 (1.05-3.77)[5)]. In a study of 2,886 American men and women 70-79 years of age, subjects with an ABI of < 0.90 displayed a higher risk of total stroke compared with those with an ABI of 0.91 to 1.30, with a multivariable HR of 1.67 (1.13-2.45)[1)]. In addition, a patient-based study of 6,880 European subjects reported that the patients with an ABI of < 0.9 had a higher risk of ischemic stroke compared with those with an ABI of > 0.90, with a multivariable HR of 1.7 (1.2-2.5)[6)].

In contrast, a meta-analysis of 16 population cohort studies demonstrated a U-shaped relationship between the ABI and total mortality, but not between the ABI and cardiovascular mortality[7)], including multivariable HRs of total mortality of 2.34 (1.97-2.78) for men with an ABI of ≤ 0.90 compared to those with an ABI of 1.11 to 1.40 and 1.38 (1.17-1.62) for men with an ABI of > 1.40 compared to those with an ABI of 1.11 to 1.20. The multi-ethnic study of atherosclerosis (MESA) also demonstrated a U-shaped association between the ABI and CVD, including multivariable HRs of CVD of 1.77 (1.31-2.40) for subjects with an ABI of < 1.00 and 1.85 (1.13-2.45) for those with an ABI of ≥ 1.40 compared to those with an ABI of 1.00 to 1.39 among 6,814 men and women 45-84 years of age[18)]. Furthermore, a recent study of 3.6 million men and women (mean age: 64.7 years), reported a U-shaped association between the ABI and a history of stroke, with a multivariable OR of 1.77 (1.72-1.82) for the subjects with an ABI of < 0.90 and 1.30 (1.22-

Table 3. Multivariable-adjusted hazard ratios for ischemic cardiovascular disease according to the ABI tertile stratified by smoking, hypertension and diabetes

	Tertiles of ABI			*p* for trend	*p* for interaction
	Low 0.54-1.17	Middle 1.08-1.17	High 1.18-1.47		
Smokers, person years	2,431	2,531	2,266		
No. of cases	42	20	16		
Multivariable HR	2.22 (1.23-4.03)†	1.13 (0.58-2.19)	1.00	0.004	
Never smokers, person years	435	398	678		
No. of cases	4	4	4		
Multivariable HR	1.53 (0.32-7.30)	2.26 (0.47-10.9)	1.00	0.58	0.37
Hypertension, person years	1,447	1,405	1,414		
No. of cases	28	11	12		
Multivariable HR	2.12 (1.04-4.30)*	0.93 (0.41-2.14)	1.00	0.02	
Non-hypertension, person years	1,420	1,525	1,529		
No. of cases	18	13	8		
Multivariable HR	2.10 (0.88-5.05)	1.62 (0.66-3.97)	1.00	0.10	0.55
Diabetes mellitus, person years	755	734	762		
No. of cases	18	5	5		
Multivariable HR	4.32 (1.52-12.3)†	1.24 (0.35-4.44)	1.00	0.002	
Non-diabetes mellitus, person years	2,112	2,187	2,181		
No. of cases	28	19	15		
Multivariable HR	1.58 (0.82-3.04)	1.22 (0.62-2.41)	1.00	0.16	0.10

*$p<0.05$, †$p<0.01$, ‡$p<0.001$ compared with the ABI >1.17 category. The variables for multivariable adjustment are similar to those in Table 2.

1.38) for the subjects with an ABI of >1.40 compared to those with an ABI of 1.00 to 1.40[19], exhibiting a similar trend to that observed in the present study.

In the current analysis, the association between a low ABI and the risk of ischemic CVD was more evident in smokers, hypertensives and diabetics, although the interactions did not reach statistical significance due to the limited number of cases in these subgroups (**Table 3**). Smoking, hypertension and diabetes are common risk factors shared by both subjects with a low ABI[10, 20] and those with a risk of ischemic CVD[14, 21], which may enhance the associations between the two conditions. A meta-analysis of 34 studies showed the importance of smoking, hypertension and diabetes as risk factors for an ABI of ≤0.90, with an OR (95% CI) of 2.1 (1.9-2.3) for current smokers, 1.5 (1.4-1.6) for hypertensives and 1.7 (1.5-1.8) for diabetics[10].

The strengths of the present cohort study include its prospective cohort design, the internal quality control protocol for data collection[11] and the standardization of the ABI measurements and other assessments[2, 13]. The limitation of this study is the use of a single baseline measurement of the ABI for the analysis, meaning that intra-subject variability in the ABI values may have attenuated the real associations. Second, the number of incident cases for total stroke, each stroke subtype and coronary heart disease was limited. Therefore, we can draw a valid conclusion only for the association between the ABI and the risk of ischemic and total CVD. Third, this study used data for elderly men from two communities, and it is uncertain whether our results are generalizable to women or middle-aged men.

In conclusion, a low ABI is associated with the risk of coronary heart disease, ischemic stroke and ischemic CVD among elderly Japanese men. Our results suggest that the ABI is a useful predictor of ischemic CVD in elderly men in the general Japanese population.

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Conflicts of Interest

All authors report no conflicts of interest.

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