Original Article

Relationship between a Low Ankle Brachial Index and All-Cause Death and Cardiovascular Events in Subjects with and without Diabetes

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Aims: The association between a low ankle brachial index (ABI) and mortality and vascular morbidity in Japanese individuals with diabetes and the independence of this association from other risk factors have not yet been examined in the primary care setting among a large number of patients.

Methods: An observational prospective cohort study was performed among 3,004 Japanese individuals (2,598 patients with diabetes) to examine all-cause death and cardiovascular disease (CVD) in relation to low ABI (<0.9) values and other risk factors.

Results: Low ABI values were found in 127 subjects (4.2%) and was associated with smoking, diabetes, hypertension, pulse pressure, glycosylated hemoglobin A1C, lipid profiles, glomerular filtration rate, uric acid and prevalent CVD at baseline. Over 13,242 person-years, 93 deaths and 117 cases of CVD occurred. In a multivariate Cox regression analysis, the hazard ratio for low-normal ABI values was 3.97 (95% CI, 2.29 to 6.88) for all-cause death and 2.86 (95% CI, 1.83-4.49) for fatal and non-fatal CVD and all-cause death. Similar hazard ratios were found when the subjects were confined to those with diabetes. All risk analyses indicated that age, a low ABI, diabetes, a history of CVD and smoking remained significantly and independently predictive of CVD and all-cause death.

Conclusions: A low ABI exhibits significant cross-sectional associations with conventional risk factors and further more with the glomerular filtration rate, uric acid level and presence of prevalent CVD at baseline, and a low ABI independently predicts subsequent death and cardiovascular events. These findings support the concept that a low ABI is an integrated marker of an excess risk of death and cardiovascular events, independent of conventional risk factors.


Key words: Ankle brachial index, Cardiovascular disease, Diabetes, Primary care, Mortality

Introduction

The ankle brachial index (ABI) represents the ratio of the ankle to brachial systolic pressure. In patients with atherosclerotic stenosis in the lower extremities, the decreased pressure in the ankle arteries results in a lower ABI. The detection of a low ABI is useful for confirming the diagnosis and severity of peripheral artery disease (PAD) in the legs and is reportedly associated with an increased risk of all-cause death and cardiovascular disease (CVD) in the general population in Western countries¹⁻⁵. The validity of a low ABI may be decreased in patients with diabetes, as the ankle pressure may be elevated due to medial arterial calcification and/or arterial stiffening, which occur more frequently in diabetes⁶. However, most prospective studies that have investigated the predictive value of a low ABI in patients with CVD...
included less than 500 subjects with diabetes\textsuperscript{3, 7, 12}, and some studies have indicated that the association between a low ABI and mortality in Caucasians is weak among subjects with diabetes compared to that observed in those without diabetes\textsuperscript{5, 8, 13}. While ethnic differences profoundly affect the prevalence of PAD\textsuperscript{10}, no such prospective studies have been performed in Japanese subjects, who are characterized by a lower prevalence of PAD than Caucasian individuals\textsuperscript{14-16}. A large-scale study of Japanese individuals including subjects with diabetes is needed to elucidate the association and predictive value of a low ABI with respect to the incidence of CVD.

In the primary care setting, screening for low ABI values is strongly recommended in subjects with diabetes, as these patients are often asymptomatic due to diabetic neuropathy, even when complicated with PAD\textsuperscript{7, 17}. However, this recommendation has not been universally embraced, and measurement of the ABI is rarely applied in routine clinical practice\textsuperscript{18}. We have obtained measurements of the ABI at the first visit to the clinic in routine clinical practice for more than 10 years. The present study investigated the cross-sectional associations between low ABI values and other cardiovascular risk factors at baseline and assessed the prognostic value of a low ABI for predicting death and cardiovascular events. This study included a large number of Japanese subjects with and without diabetes and explored whether the impact of a low ABI on outcomes is independent of other cardiovascular risk factors.

**Subjects and Methods**

**Patient Recruitment**

A prospective cohort study was performed to investigate the associations between low ABI values and cardiovascular risk factors at baseline and whether a low ABI is predictive of all-cause death and cardiovascular events independent of other risk factors. The health care system in Japan provides healthcare services with the patient accepting responsibility for 30\% of the cost and the government paying the remaining 70\%. Payment for personal medical services is offered through a universal health care insurance system that provides relative equality of access. Patients are free to select physicians or facilities of their choice. All consecutive patients 20 years of age or older who visited the outpatient clinic of Jiyugaoka Internal Medicine between 2001 and 2011 were enrolled in this study. The study was performed in a primary care setting. All of the subjects, most of whom had type 2 diabetes, hypertension or dyslipidemia, underwent ABI measurement at their first visit as a baseline routine examination ($N=3501$). Subjects who discontinued the visits within three months, primarily due to visiting other hospitals or moving to other cities, were excluded, leaving 3,004 subjects (non-diabetes: 406, type 2 diabetes: 2,572, type 1 diabetes: 26) eligible for this cohort. Those who discontinued visits were similar to the remaining patients with respect to clinical features. The study protocol was approved by the local ethics committee and carried out in accordance with the Helsinki Declaration II.

**Baseline Examinations**

A short physical examination and medical history assessment were performed at baseline in each patient. The presence of prevalent CVD at baseline included a history of coronary heart disease (CHD), cerebrovascular disease and/or PAD. The definition of CVD was the same as that described below. The smoking status was defined as current or not. Type 2 and type 1 diabetes was defined according to the Japan Diabetes Society criteria. Blood pressure (BP) was measured in the sitting position after a rest of more than five minutes. Hypertension was defined as a BP of $\geq 140/90$ mmHg or the current use of antihypertensive agents. Non-fasting blood samples were obtained for measurements of the glycosylated hemoglobin A\textsubscript{1c} level (HbA\textsubscript{1c}, normal range: 4.6-6.2\%) and serum creatinine (Cr), uric acid and lipid concentrations. Dyslipidemia was defined as a serum concentration of total cholesterol of $\geq 220$ mg/dL, triglycerides of $\geq 150$ mg/dL, or high-density lipoprotein (HDL) cholesterol of $< 40$ mg/dL and/or the current use of lipid-lowering agents. The non-HDL cholesterol level was calculated by subtracting the HDL cholesterol level from the total cholesterol level. The serum concentration of Cr was measured using an enzymatic method. The estimated glomerular filtration rate (eGFR) was calculated using the following equation proposed by the Japanese Society of Nephrology: $\text{eGFR (ml/min per 1.73 m}^2\text{)} = 194 \times \text{(age [years])}^{-0.287} \times \text{(serum Cr [mg/dL])}^{-1.094} \times 0.739$ (if female).

The ABI was measured at baseline under standardized conditions. Doppler-assisted systolic blood pressure measurements were obtained from the brachial and posterior tibial arteries on both sides using 12-cm cuffs (Colin Co., Ltd., Komaki, Japan). The ABI was calculated for each leg using the highest ankle pressure divided by the highest systolic brachial pressure. An ABI of $<0.9$ in either leg was considered abnormal. Although an ABI of $>1.4$ has been indicated to be abnormally high as a result of poor arterial compressibility due to arterial stiffening and calcifica-
tion3, there were only 16 subjects in this cohort; therefore, this parameter was not defined separately.

**Main Outcomes**

The subjects attended the clinic monthly and were followed from the baseline visit until the end of observation (August, 2012) or an event. Fatal and non-fatal CVD events included onset of coronary heart disease (CHD), ischemic cerebrovascular stroke and PAD. Information regarding the onset of cardiovascular events and the cause of death was provided by the medical doctors (e.g., cardiologists, neurologists and vascular surgeons) who managed the event. Three outcomes were assessed: 1) all-cause death, 2) the occurrence of cardiovascular events and 3) composite endpoints, including death and the occurrence of cardiovascular events.

**Diagnosis of CVD**

Non-fatal CHD included acute myocardial infarction with survival of more than 24 hours after the onset of symptoms, percutaneous coronary intervention, coronary artery bypass and new-onset unstable angina pectoris. A non-fatal ischemic stroke was defined as an acute focal neurological deficit lasting for longer than 24 hours. PAD was diagnosed in cases involving intermittent claudication with confirmation of an ABI of <0.9 or significant peripheral artery stenosis on angiography and/or leg amputation above the ankle due to diabetes. We classified sudden death as a cardiovascular event, unless there was a clear non-vascular cause. An independent panel, working with the endpoint adjudication committee, assessed all potential endpoints and classified them in accordance with the predefined criteria.

**Statistical Analysis**

The data are expressed as the mean ± SD, unless otherwise stated. For comparisons between two groups, unpaired Student’s t-test, the Mann-Whitney U test for variables with a skewed distribution and the χ² test for categorical variables were used. A logistic regression analysis was used to assess the associations between the baseline risk factors and the concomitant presence of a low ABI following adjustment for the traditional cardiovascular risk factors of age, sex, BMI and smoking status. The follow-up time was calculated as the time between the baseline examination and either the date of the main outcome or the end of observation (December 31, 2011). For subjects who discontinued clinic attendance, the date of the final visit in cases in which no occurrence of events was confirmed was employed. The time to event distribution according to the ABI group was summarized with Kaplan-Meier curves. Cox regression models examining the effects of a low ABI on each event rate were adjusted for potential confounders. As to potential confounders, the conventional risk factors of age sex, BMI and smoking status were entered in the model, and diabetes, hypertension, dyslipidemia, eGFR and a past history of CVD were additionally considered. P-values under 5% (two-tailed) were considered to be significant. All analyses were performed using the statistical software package SPSS (SPSS Japan Inc., Tokyo, Japan).

**Results**

**Baseline Data**

Among the 3,004 subjects, 127 (4.2%) had low ABI values, including four patients with symptoms of PAD. Table 1 shows the baseline characteristics according to the ABI group. The patients with a low ABI were significantly older and had higher rates of diabetes, hypertension and a history of CHD, stroke and PAD, higher pulse pressure values and non-HDL cholesterol, triglyceride and uric acid levels and lower DBP, HDL and eGFR values. Data were available for 98.5% or more of the patients. The prevalence of a low ABI among the subjects with diabetes was 4.6% (120/2598), which was significantly higher than the 1.7% (7/406) observed in those without diabetes (p = 0.01). Smoking was significantly associated with a low ABI following adjustment for age, sex and body mass index (BMI) (OR 1.87, 95%CI 1.27-2.77, p < 0.001). A logistic regression analysis performed following adjustment for age, sex, BMI and smoking revealed that a low ABI was significantly associated with diabetes, a history of CHD, stroke and PAD, higher pulse pressure values and HbA1c, non-HDL cholesterol, triglyceride and uric acid levels and lower diastolic pressure, HDL cholesterol and eGFR values.

**Follow-Up**

During a mean observation period of 4.4 years (range, 0.3-11.7), 93 deaths and 117 cardiovascular events (coronary heart disease: 39, stroke: 52, PAD: 5, sudden death: 21) occurred. A total of 866 subjects (28.8%) were lost to follow-up before reaching the end of study period in whom being free from events until the final visit was confirmed. The incidence of each outcome according to the ABI group is shown in Table 2. Compared with the subjects with an ABI of ≥ 0.9, those with an ABI of <0.9 had a significantly increased risk of an outcome event. When the analysis was confined to subjects with diabetes, a low ABI was
ABI and Cardiovascular Disease in Diabetes and Non-Diabetes

The hazard ratios for the composite endpoint are shown in Table 3. The multivariate Cox regression analysis including all variables in Table 3 revealed age, a low ABI, diabetes, a history of CVD and smoking to be independently and significantly predictive of the outcome. In order to explore the effects of a low ABI found to exhibit independent associations with all three outcomes (adjusted HR [95% CI]; 4.15 (2.34-7.34); 2.50 (1.41-4.42); 2.85 (1.80-4.51), respectively for each outcome), which remained significant, even after adjustment for diabetes, hypertension, dyslipidemia, eGFR and a past history of CVD, in addition to age, sex, BMI and smoking. The times to event for all-cause death and the composite endpoint of cardiovascular events and all-cause death according to the ABI group are illustrated with Kaplan-Meier curves (Fig. 1).
The prevalence of diabetes and the number of elderly subjects with diabetes are also increasing in Japan, and 30-40% of people with diabetes smoke. Only 3.1% (4/127) of such patients had symptoms of PAD among the subjects with a low ABI in this study, and underdiagnosis of PAD in primary care practice can be a barrier to effective secondary prevention of the high ischemic cardiovascular risks associated with PAD. Therefore, screening for low ABI values in routine clinical practice will become more important and possibly essential, particularly in individuals with diabetes and those receiving care for primary prevention of CVD.

The present study only incorporated the baseline measurements of ABI and other cardiovascular risk factors. Approximately 30-50% of the subjects had already received blood pressure- and/or lipid-lowering agents at baseline. This study did not investigate the effects of treatment, and further treatment was administered during the follow-up period (data not shown). It is presumed that a low ABI at baseline remains a risk factor for a poor outcome, even after the administration of aggressive treatment, which further reinforces the importance of routinely measuring the ABI.

We found that the detection of a low ABI in routine clinical practice is highly predictive of all-cause death and cardiovascular events based on the results of our large-scale study of Japanese individuals, including subjects with and without diabetes. The predictive effect was significant and independent not only of conventional risk factors, but also a low eGFR and prevalent CVD, and remained significant in the subjects without a history of CVD. This study suggests that, even in a population characterized by a lower prevalence of obesity and PAD and a lower incidence of CHD and PAD, the detection of a low ABI is useful for identifying diabetic subjects that should be targeted for multifactorial intensive treatment in the primary care setting in terms of improving all-cause mortality and cardiovascular morbidity.

The prevalence of PAD is higher in individuals with diabetes than in those without, as observed in this and other studies, and is reportedly increasing. The prevalence of diabetes and the number of elderly subjects with diabetes are also increasing in Japan, and 30-40% of people with diabetes smoke. Only 3.1% (4/127) of such patients had symptoms of PAD among the subjects with a low ABI in this study, and underdiagnosis of PAD in primary care practice can be a barrier to effective secondary prevention of the high ischemic cardiovascular risks associated with PAD. Therefore, screening for low ABI values in routine clinical practice will become more important and possibly essential, particularly in individuals with diabetes and those receiving care for primary prevention of CVD.

**Discussion**

We found that the detection of a low ABI is strongly associated with outcomes and is predictive of all-cause death and cardiovascular events based on the results of our large-scale study of Japanese individuals, including subjects with and without diabetes. The predictive effect was significant and independent not only of conventional risk factors, but also a low eGFR and prevalent CVD, and remained significant in the subjects without a history of CVD. This study suggests that, even in a population characterized by a lower prevalence of obesity and PAD and a lower incidence of CHD and PAD, the detection of a low ABI is useful for identifying diabetic subjects that should be targeted for multifactorial intensive treatment in the primary care setting in terms of improving all-cause mortality and cardiovascular morbidity.

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We found a low ABI to be a risk factor, independent of other cardiovascular risk factors. Only a few studies have investigated the predictive value of a low ABI according to the presence or absence of CVD risk factors. In the present study, a low ABI was found to be an independent significant risk factor among
Several limitations of the present study should be mentioned. First, we should acknowledge the small number of events in the non-diabetic subjects, who demonstrated a lower prevalence of a low ABI. Second, the generalizability of the subjects should be discussed. The incidence of all-cause death and cardiovascular events observed in the subjects with and without diabetes in this cohort was slightly lower and/or almost the same as that observed in Japanese populations reported in other studies23-26). These facts support the generalizability of the cohort. Third, approximately 29% of the participants were lost to follow-up because they moved to other cities/clinics or discontinued clinic attendance. We were unable to evaluate their further outcomes because no regional or national registries for death and disease identification systems are available in Japan. In order to minimize this inherent problem, a life-table analysis was used to cover the

subjects with an age of ≥70, hypertension, a BMI of <25 and no history of CVD, which is in agreement with the findings of some, but not all previous studies3,12), whereas most other studies did not specifically examine this issue. While the present subjects with a low ABI more often exhibited a history of CVD, we found that a low ABI was predictive of CVD among the subjects without prevalent CVD.

It was interesting to find an association between hyperuricemia and a low ABI in the baseline analysis. This is the first report of such an association to our knowledge, and the results are in line with the findings of several studies showing a relationship between the serum uric acid level and the development of atherosclerotic disease20,21). A significant association between a reduced eGFR and a low ABI has previously been reported22), and this finding was confirmed in our study at baseline.

### Table 3. Association of a low ABI and cardiovascular risk factors with subsequent development of the composite endpoint (all-cause death and cardiovascular events)

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>No.</th>
<th>PY* at risk</th>
<th>No. of cases</th>
<th>Incidence (95%CI)</th>
<th>HR of risk factor (adjusted, 95%CI)</th>
<th>HR of low ABI (adjusted, 95%CI)</th>
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</thead>
<tbody>
<tr>
<td>Age (≥ 70 yr)</td>
<td>No 2473</td>
<td>10971</td>
<td>108</td>
<td>9.8 (8.1-11.9)</td>
<td>3.11 (2.20-4.41)</td>
<td>1.14 (0.45-2.88)</td>
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<tr>
<td></td>
<td>Yes 531</td>
<td>2013</td>
<td>73</td>
<td>36.3 (28.5-45.4)</td>
<td>2.52 (1.54-4.12)</td>
<td>3.75 (2.04-6.90)</td>
</tr>
<tr>
<td>ABI &lt; 0.9</td>
<td>No 2877</td>
<td>12589</td>
<td>156</td>
<td>12.1 (10.3-14.2)</td>
<td>2.41 (1.18-4.94)</td>
<td>2.29 (0.10-50.68)</td>
</tr>
<tr>
<td></td>
<td>Yes 127</td>
<td>396</td>
<td>25</td>
<td>63.1 (41.3-91.8)</td>
<td>1.87 (1.24-2.82)</td>
<td>2.22 (1.32-3.73)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No 406</td>
<td>1483</td>
<td>8</td>
<td>5.4 (2.3-10.6)</td>
<td>1.42 (1.02-1.97)</td>
<td>2.16 (1.16-4.01)</td>
</tr>
<tr>
<td></td>
<td>Yes 2598</td>
<td>11501</td>
<td>173</td>
<td>15.0 (12.9-17.4)</td>
<td>1.44 (1.11-1.83)</td>
<td>1.77 (0.83-3.77)</td>
</tr>
<tr>
<td>History of CVD</td>
<td>No 2822</td>
<td>12262</td>
<td>193</td>
<td>15.7 (13.6-18.1)</td>
<td>1.87 (1.24-2.82)</td>
<td>2.99 (1.55-5.79)</td>
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<td></td>
<td>Yes 181</td>
<td>723</td>
<td>39</td>
<td>53.9 (38.6-73.0)</td>
<td>1.21 (1.04-1.41)</td>
<td>1.77 (0.83-3.77)</td>
</tr>
<tr>
<td>Smoking (current)</td>
<td>No 1961</td>
<td>8448</td>
<td>116</td>
<td>13.7 (11.4-16.4)</td>
<td>1.42 (1.02-1.97)</td>
<td>2.16 (1.16-4.01)</td>
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<tr>
<td></td>
<td>Yes 998</td>
<td>4506</td>
<td>65</td>
<td>14.4 (11.1-18.3)</td>
<td>1.43 (1.09-1.86)</td>
<td>2.40 (1.03-5.59)</td>
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<tr>
<td>eGFR (&lt; 60 ml/min/1.73 m^2)</td>
<td>No 2555</td>
<td>11145</td>
<td>128</td>
<td>11.5 (9.6-13.6)</td>
<td>1.43 (0.99-2.07)</td>
<td>2.51 (1.21-5.19)</td>
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<tr>
<td></td>
<td>Yes 425</td>
<td>1799</td>
<td>53</td>
<td>29.5 (22.1-38.4)</td>
<td>2.35 (1.60-3.48)</td>
<td>2.53 (1.30-4.93)</td>
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<td>Hypertension</td>
<td>No 1314</td>
<td>5074</td>
<td>60</td>
<td>11.8 (9.0-15.2)</td>
<td>1.35 (0.97-1.88)</td>
<td>2.96 (1.09-7.98)</td>
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<tr>
<td></td>
<td>Yes 1687</td>
<td>7203</td>
<td>121</td>
<td>16.8 (14.0-20.0)</td>
<td>1.06 (0.77-1.49)</td>
<td>2.49 (1.44-4.32)</td>
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<tr>
<td>BMI (≥ 30 kg/m^2)</td>
<td>No 2596</td>
<td>11299</td>
<td>158</td>
<td>14.0 (11.9-16.3)</td>
<td>1.06 (0.77-1.49)</td>
<td>3.21 (1.90-5.42)</td>
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<td></td>
<td>Yes 408</td>
<td>1685</td>
<td>23</td>
<td>13.6 (8.7-20.4)</td>
<td>0.94 (0.36-2.46)</td>
<td>1.94 (0.20-19.5)</td>
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<td>Male sex</td>
<td>No 1957</td>
<td>8771</td>
<td>132</td>
<td>15.1 (12.6-17.8)</td>
<td>1.07 (0.89-1.28)</td>
<td>2.53 (1.44-4.45)</td>
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<tr>
<td></td>
<td>Yes 1047</td>
<td>4214</td>
<td>49</td>
<td>11.6 (8.6-15.4)</td>
<td>1.22 (1.00-1.48)</td>
<td>2.92 (1.04-8.23)</td>
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<td>Dyslipidemia</td>
<td>No 1068</td>
<td>4726</td>
<td>80</td>
<td>16.9 (13.4-21.0)</td>
<td>0.72 (0.53-1.01)</td>
<td>4.14 (1.89-9.10)</td>
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<td>Yes 1936</td>
<td>8258</td>
<td>101</td>
<td>12.2 (10.0-14.8)</td>
<td>1.98 (1.05-3.72)</td>
<td>-</td>
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</table>

The hazard ratio of each risk factor is indicated as the result of a Cox regression analysis adjusted for all variables in the Table. The hazard ratio of a low ABI according to the presence or absence of each risk factor is simultaneously indicated as the result of a Cox regression analysis adjusted for all variables in the Table.

*PY: person-years
censored cases. Finally, whether an ABI of $>1.4$ occurs more commonly in subjects with diabetes and is associated with mortality requires further investigation.

In conclusion, the present study suggests that a low ABI is an integrated marker of tissue/vascular damage affected by age, smoking, blood pressure, blood glucose, lipids, uric acid, the renal function and prevalent CVD, indicating its role as an excess and independent risk factor for all-cause death and cardiovascular events.

Disclosures

None.

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