Clinical Impact of the Ankle-Brachial Index in Patients Undergoing Successful Percutaneous Coronary Intervention

Seiichi Hiramori, MD; Yoshimitsu Soga, MD; Norihiko Kamioka, MD; Takashi Miura, MD; Tatsuki Doijiri, MD; Shinichi Shirai, MD; Kenji Ando, MD

Background: Several studies have reported a relationship between clinical outcomes and the ankle-brachial index (ABI) in different populations. However, the relationship in Japanese patients or in patients undergoing percutaneous coronary intervention (PCI) has not been examined well.

Methods and Results: The subjects were 1,857 patients who underwent PCI from July 2007 to May 2010 and in whom the carotid and renal arteries and abdominal aorta were examined simultaneously by ultrasonography and ABI. We investigated the relationship between ABI and major adverse cardiovascular events (MACE: all-cause death, myocardial infarction, and stroke). The median follow-up was 1,322 days (interquartile range: 1,092–1,566 days). Patients with low (<0.9), borderline (0.9–1.0) and high ABI (>1.4) had significantly higher incidence of MACE at 4 years (31%, 15%, 10%, and 29% for the low, borderline, normal, and high groups, respectively; log-rank P<0.0001) and all-cause mortality at 4 years (22%, 12%, 6.9%, and 29%, respectively; P<0.0001) compared with the normal ABI group (1.0 ≤ ABI ≤ 1.4). The adjusted hazard ratios for MACE were 2.35 (1.72–3.20), 1.27 (0.89–1.80) and 1.87 (0.81–3.79) for low, borderline and high ABI, respectively.

Conclusions: This study suggested that ABI provides additional information for cardiovascular disease risk stratification in Japanese patients undergoing PCI, even it is borderline ABI.

Key Words: Ankle-brachial index; Cardiovascular outcome; Ischemic heart disease

The ankle-brachial index (ABI) is a simple and non-invasive tool that is recommended as a screening test in the Trans-Atlantic Inter-Society Consensus (TASC) II guideline. In several clinical settings, both high and low ABI values have been reported to be associated with cardiovascular outcomes. In addition, the presence of polyvascular disease has been associated with increased mortality and morbidity in patients undergoing percutaneous coronary intervention (PCI). Therefore, the measurement of ABI is recommended to examine for systemic atherosclerosis in patients with ischemic heart disease (IHD). Recently, it was proposed that ABI 0.9–1.0, which was previously defined as normal, should be considered as borderline ABI. However, there is a paucity of data about the association between ABI and clinical outcomes in Japanese patients undergoing PCI. Accordingly, the objective of this study was to investigate this relationship and also address the importance of borderline ABI in Japanese patients.
study protocol was approved by the institutional review board of the hospital and conducted in accordance with the Declaration of Helsinki.

Measurement and Definition of ABI
Bilateral arm and ankle systolic pressures were simultaneously taken with the subject in a supine position. Bilateral ankle pressures were then normalized to the higher brachial pressure of either arm to calculate the ABI. The worst of the bilateral values was used to define the ABI for each individual. In patients who received maintenance hemodialysis (HD), blood pressure (BP) in the brachial artery was taken only on the non-dialysis shunt side. In this study, ABI was measured with a BP-203RPEIII automated oscillometric device (OMRON Corp., Kyoto, Japan). The interobserver variability of the oscillometric method was reported to have a coefficient of variation of 11% in the ARIC study.9

Normal ABI was defined values of 1.0–1.4 detected on both sides. Low ABI was defined as <0.9 on 1 or both sides, based on previous studies showing that this threshold has a sensitivity and specificity of approximately 80% and 90%, respectively, to detect PAD compared with angiography.9 High ABI corresponded to a value >1.4, which has been reported to predict the incidence of PAD from 60–80%.1111 Borderline ABI was defined as 0.9–1.0 in accordance with the AHA/ACC guideline.7

Other Definitions
Hypertension (HT) was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or ongoing treatment for HT. Dyslipidemia was defined as a serum total cholesterol concentration ≥220 mg/dL, a low-density lipoprotein-cholesterol concentration ≥140 mg/dL, or current treatment with lipid-lowering drugs. Diabetes was defined as Hba1c >6.5%, a casual plasma glucose >200 mg/dL, or current treatment with oral hypoglycemic agents or insulin injection. Left ventricular ejection fraction (LVEF) was measured on echocardiography and LVEF <40% was regarded as LV dysfunction. Chronic kidney disease (CKD) was defined as an estimated creatinine clearance <30 mL/min based on the Cockcroft-Gault formula.

Follow-up and Endpoints
Patients were re-examined after 6 and 12 months and annually thereafter during an office visit or by telephone interview. The following data were systematically retrieved: death, the occurrence of fatal and non-fatal myocardial infarction (MI), and stroke or transient ischemic attack.

The primary endpoint of this study was the incidence of major adverse cardiovascular events (MACE; all-cause death, MI and stroke) at 4 years. Secondary endpoints were each of the clinical outcomes (all-cause death, MI or stroke) at 4 years.

Statistical Analysis
Baseline demographic and clinical characteristics are summarized as mean and standard deviation or median and interquartile range (IQR) for continuous variables, as appropriate, and as frequencies and percentages for categorical variables. Comparisons among the ABI groups were performed using ANOVA, Kruskal-Wallis and Pearson chi-square test, where appropriate. Survival curves according to ABI were constructed with Kaplan-Meier estimates and compared by the log-rank test. Low, borderline and high ABI groups were compared with a reference group of normal ABI. Bonferroni’s correction was applied when multiple comparisons were performed. P<0.017 (0.05÷3) was considered indicative of a statistically significant difference among the 3 groups. For the primary outcome, we used a Cox proportional hazard regression model to evaluate the effect of ABI. On univariate analysis, ABI group was used as an independent variable along with the following variables: age >70 years, sex, body mass index (BMI) <18.5, HT, dyslipidemia, diabetes mellitus (DM), current smoker, CKD, HD, LV dysfunction, medications (antiplatelet agents, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin-receptor blockers (ARBs), β-blockers, calcium-channel blockers, statins, diuretics). Variables that showed P<0.10 on univariate analysis were entered into a multivariate forward stepwise (P<0.05 for entering and excluding) Cox proportional hazards regression analysis. In addition, hazard ratios (HRs) for ABI, subdivided into 8 categories compared with a reference range of 1.21–1.30, which is the median value of the normal ABI, were obtained for MACE. Subgroup analyses were performed to investigate the interaction between ABI and atrial fibrillation (AF) or between ABI and HD. P<0.05 was considered statistically significant. All data analyses were performed with JMP 9.0.2 software (SAS Institute, Cary, NC, USA).

Results
Study Population and Baseline Characteristics
The subjects in this study were 2,052 patients. Subjects were excluded if essential data for categorization was missing or if they had previously undergone EVT for PAD or surgery for AAA, as follows: missing baseline ABI data (n=39); a history of EVT for PAD or surgery for AAA (n=121); missing baseline characteristics data (n=1). In addition, taking the influence of Hill’s sign into consideration, subjects who had severe aortic regurgitation on cardiac ultrasonography (n=1) or did not have their aortic valve evaluated by cardiac ultrasonography (n=33) were excluded, resulting in 1,857 patients included in the analyses.

Table 1 shows the baseline characteristics by ABI group. The low ABI group was older than the other 3 groups. The proportion of acute coronary syndrome was similar among groups. Although there were some differences with respect to cardiovascular disease risk factors, such as HT, dyslipidemia, DM and current smoker, among groups, they were not distributed in any specific group. The high ABI group had more patients who were dependent on HD and took less statins compared with the other groups.

Outcomes
During the median follow-up of 1,322 days (IQR 1,092–1,566 days), 70 patients (29%) in the low ABI group, 42 (14%) in the borderline ABI group, 120 (9.4%) in the normal ABI group and 8 (28%) in the high ABI group had MACE.

Patients with low, borderline or high ABI had a significantly higher incidence of MACE at 4 years (31%, 15%, 10%, and 29% for the low, borderline, normal, and high groups, respectively; log-rank P<0.0001; Figure 1) and of all-cause death at 4 years (22%, 12%, 6.9%, and 29%; P<0.0001; Figure 2) compared with the normal ABI group. Regarding the incidence of MI (6.4%, 1.5%, 2.4%, and
Table 1. Baseline Characteristics of Japanese Patients Undergoing PCI

<table>
<thead>
<tr>
<th>Variables</th>
<th>Low ABI (n=250)</th>
<th>Borderline ABI (n=312)</th>
<th>Normal ABI (n=1,300)</th>
<th>High ABI (n=29)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>74.2 (9.0)</td>
<td>69.5 (10.7)</td>
<td>69.1 (9.7)</td>
<td>64.8 (12.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age &gt;70 years, n (%)</td>
<td>177 (72)</td>
<td>164 (54)</td>
<td>598 (47)</td>
<td>10 (34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex (male), n (%)</td>
<td>182 (74)</td>
<td>227 (74)</td>
<td>961 (75)</td>
<td>23 (79)</td>
<td>0.91</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>22.9 (3.8)</td>
<td>24.2 (3.4)</td>
<td>24.0 (3.2)</td>
<td>22.8 (3.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI &lt;18.5, n (%)</td>
<td>29 (12)</td>
<td>10 (3)</td>
<td>40 (3)</td>
<td>4 (14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ABI, mean (SD)</td>
<td>0.72 (0.14)</td>
<td>0.96 (0.03)</td>
<td>1.12 (0.07)</td>
<td>1.56 (0.14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ACS, n (%)</td>
<td>45 (18)</td>
<td>62 (20)</td>
<td>209 (16)</td>
<td>5 (17)</td>
<td>0.43</td>
</tr>
<tr>
<td>HT, n (%)</td>
<td>211 (86)</td>
<td>256 (84)</td>
<td>1,017 (80)</td>
<td>18 (62)</td>
<td>0.004</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>120 (49)</td>
<td>184 (60)</td>
<td>763 (60)</td>
<td>11 (38)</td>
<td>0.002</td>
</tr>
<tr>
<td>DM, n (%)</td>
<td>130 (53)</td>
<td>156 (51)</td>
<td>543 (43)</td>
<td>14 (48)</td>
<td>0.003</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>64 (26)</td>
<td>71 (23)</td>
<td>263 (21)</td>
<td>9 (31)</td>
<td>0.149</td>
</tr>
<tr>
<td>HD, n (%)</td>
<td>28 (11)</td>
<td>20 (6.5)</td>
<td>46 (3.6)</td>
<td>14 (48)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CKD, n (%)</td>
<td>162 (66)</td>
<td>156 (51)</td>
<td>524 (41)</td>
<td>20 (69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OMI, n (%)</td>
<td>58 (24)</td>
<td>82 (27)</td>
<td>358 (28)</td>
<td>7 (24)</td>
<td>0.53</td>
</tr>
<tr>
<td>LV dysfunction, n (%)</td>
<td>35 (19)</td>
<td>21 (9.8)</td>
<td>54 (5.9)</td>
<td>3 (17)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>40 (16)</td>
<td>29 (9.5)</td>
<td>93 (6.9)</td>
<td>2 (6.9)</td>
<td>0.0004</td>
</tr>
<tr>
<td>Aspirin, n (%)</td>
<td>234 (96)</td>
<td>293 (96)</td>
<td>1,229 (96)</td>
<td>24 (83)</td>
<td>0.051</td>
</tr>
<tr>
<td>Thienopyridine, n (%)</td>
<td>220 (90)</td>
<td>277 (91)</td>
<td>1,131 (89)</td>
<td>22 (76)</td>
<td>0.165</td>
</tr>
<tr>
<td>ACEI/ARB, n (%)</td>
<td>155 (63)</td>
<td>186 (61)</td>
<td>703 (55)</td>
<td>12 (41)</td>
<td>0.01</td>
</tr>
<tr>
<td>CCB, n (%)</td>
<td>108 (44)</td>
<td>131 (43)</td>
<td>562 (44)</td>
<td>9 (31)</td>
<td>0.55</td>
</tr>
<tr>
<td>β-blocker, n (%)</td>
<td>75 (31)</td>
<td>90 (29)</td>
<td>367 (29)</td>
<td>7 (24)</td>
<td>0.87</td>
</tr>
<tr>
<td>Statin, n (%)</td>
<td>123 (50)</td>
<td>178 (58)</td>
<td>748 (59)</td>
<td>7 (24)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Diuretics, n (%)</td>
<td>79 (32)</td>
<td>74 (24)</td>
<td>166 (13)</td>
<td>3 (10)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Continuous data are presented as mean (standard deviation) and categorical data as number (%). ABI, ankle-brachial index; ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BMI, body mass index; CCB, calcium-channel blocker; CKD, chronic kidney disease; DM, diabetes mellitus; HD, hemodialysis; HT, hypertension; LV, left ventricular; OMI, old myocardial infarction; PCI, percutaneous coronary intervention.

Figure 1. Time to MACE according to baseline ABI group. Normal ABI group showed significantly better outcomes than the other groups. ABI, ankle-brachial index; MACE, major adverse cardiovascular events.
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4.6%; P=0.001; Figure 3) and of stroke (9.9%, 3.4%, 2.3%, and 0%; P<0.0001; Figure 4), the low ABI group was significantly higher than the normal ABI group at 4 years.

On univariate Cox proportional hazards regression analysis for the primary outcome, age > 70 years (HR 2.14, 95% confidence interval [CI] 1.64–2.82, P<0.0001), BMI <18.5 (HR 3.50, 95% CI 2.33–5.08; P<0.0001), CKD (non-HD; HR 2.04, 95% CI 1.55–2.70, P<0.0001), HD (HR 5.10, 95% CI 3.39–7.50, P<0.0001), LV dysfunction (HR 1.99, 95% CI 1.29–2.94, P=0.002), use of ACEIs/ARBs (HR 1.34, 95% CI 1.03–1.74, P=0.03), non-use of statins (HR 1.85, 95% CI 1.38–2.45, P<0.0001), and ABI group (low ABI: HR 3.50, 95% CI 2.59–4.67, P<0.0001; border-
Relationship Between ABI and Clinical Outcomes

This study retrospectively investigated the clinical effect of ABI in 1,857 patients with IHD undergoing PCI. The main findings of the present study were as follows: (1) patients with IHD undergoing PCI in both the high ABI and low ABI groups had higher incidences of MACE and all-cause death compared with the normal ABI group; the low ABI group had significantly higher incidence of MI and stroke compared with the normal ABI group; (2) even the borderline ABI group had higher incidence of MACE and all-cause death compared with the normal ABI group; (3) after adjustment for multivariable factors, low ABI (HR 2.35, 95% CI 1.72–3.20; P<0.0001) was a significant predictor of MACE. Borderline and high ABI tended to lead to an increased likelihood of MACE, but it was not significant (borderline ABI: HR 1.27, 95% CI 0.89–1.80, P=0.187; high ABI: HR 1.87, 95% CI 0.81–3.79, P=0.133).

In addition, we investigated the unadjusted relative risk of MACE according to ABI subgroups. When the reference ABI was 1.21–1.30, the HR for MACE formed a nearly U-shaped distribution (Figure 5).

Finally, subgroup analyses were performed to investigate the interaction between ABI and AF, and between ABI and HD. Irrespective of AF or HD, similar tendencies were observed in all subgroups (Figure 6).

Discussion

This study retrospectively investigated the clinical effect of ABI in 1,857 patients with IHD undergoing PCI. The main findings of the present study were as follows: (1) patients with IHD undergoing PCI in both the high ABI and low ABI groups had higher incidences of MACE and all-cause death compared with the normal ABI group; the low ABI group had significantly higher incidence of MI and stroke compared with the normal ABI group; (2) even the borderline ABI group had higher incidence of MACE and all-cause death compared with the normal ABI group; (3) after adjustment for multivariable factors, low ABI was an
significantly higher internal carotid artery intima-media thickness was observed not only in the definite ABI group, defined as an ABI <0.90, but also in the borderline ABI group, defined as ABI 0.90–0.99 and the low normal ABI group, defined as ABI 1.00–1.09. As the ABI was lower in this study, a higher internal carotid artery intima-media thickness was observed. In the meantime, it has been reported that subjects with high ABI should be considered as PAD-equivalent because occlusive PAD is highly prevalent. Given these findings, all ABI groups, other than the normal ABI group, could develop atherosclerosis in a non-coronary vascular bed. As shown in previous studies, the presence of polyvascular disease is associated with MACE in patients undergoing PCI. Accordingly, the HRs for MACE might form a U-shaped curve.

Study Limitations
First, this was a retrospective study, and uncontrolled confounding factors might have contributed to our findings. Second, it was a single-center observational study, and the number of patients in the high ABI group was very small. Third, the subjects of this study were only Japanese. However, previous studies have investigated the relationship between clinical outcome and ABI group in other populations. Hence, the present study is significant in demonstrating an association between clinical outcomes and the ABI in Japanese patients undergoing PCI. Fourth, diagnostic imaging was not necessarily performed to confirm the presence of PAD in this study. For this reason, the relationship between ABI and the presence of PAD was unclear. Finally, there is a possibility that several factors may affect the measurement of ABI. However, ABI is a simple and noninvasive tool, and its versatility plays an important role in daily clinical practice.

In conclusion, the present study demonstrated a...
U-shaped relationship between ABI and MACE, which suggests that ABI provides additional information on CVD risk stratification in patients undergoing PCI.

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Disclosures
All authors have nothing to disclose.

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