Ankle-Brachial Blood Pressure Index Predicts All-Cause and Cardiovascular Mortality in Hemodialysis Patients

KUMEONO,* AKIYASTUCHIDA,† HIRONOBUKAWAI,‡ HIDENEROMATSU,§ RYOUJIKAWAMATSU,§ AKIRAMEZAWA,¶ SHINTAROUMAN,¶¶ TOMOYUKIKAWADA,# and YOSHIHISANOJIMA@ for the GUNMA Dialysis and ASO Study Group

*Kanetsu Chuohospital, †Toho Hospital, ‡Maebashi Saiseikai Hospital, §Hidaka Hospital, ¶Nishitakakai Clinic, ¶Wakaba Hospital, ¶¶ Hirosegawa Clinic, #Department of Public Health, Gunma University School of Medicine, and @Third Department of Internal Medicine, Gunma University School of Medicine, Maebashi, Japan.

Abstract. A reduction in ankle-brachial BP index (ABPI) is associated with generalized atherosclerotic diseases and predicts cardiovascular mortality and morbidity in several patient populations. However, a large-scale analysis of ABPI is lacking for hemodialysis (HD) patients, and its use in this population is not fully validated. A cohort of 1010 Japanese patients undergoing chronic hemodialysis was studied between November 1999 and May 2002. Mean age at entry was 60.6 ± 12.5 yr, and duration of follow-up was 22.3 ± 5.6 mo. Patients were stratified into five groups (< 0.9, ≥ 0.9 to < 1.0, ≥ 1.0 to < 1.1, ≥ 1.1 to < 1.3, and ≥ 1.3) by ABPI measured at entry by an oscillometric method. The frequency distribution of ABPI was 16.5% of patients < 0.9, 8.6% of patients ≥ 0.9 to < 1.0, 16.9% of patients 1.0 to < 1.1, and 47.0% of patients ≥ 1.1 to < 1.3, whereas 10.9% of patients had an abnormally high ABPI (≥ 1.3). The relative risk of a history of diabetes mellitus (DM), cardiovascular, and cerebrovascular disease was significantly higher in patients with lower ABPI than those with ABPI ≥ 1.1 to < 1.3. During the study period, 77 cardiovascular and 41 noncardiovascular fatal events occurred. On the basis of Cox proportional hazards regression analysis, ABPI emerged as a strong independent predictor of all-cause and cardiovascular mortality. After adjustment for confounding variables, the hazard ratio (HR) for ABPI < 0.9 was 4.04 (95% confidence interval, 2.38 to 6.95) for all-cause mortality and 5.90 (2.83 to 12.29) for cardiovascular mortality. Even those with modest reductions in the ABPI (≥ 0.9 to < 1.1) appeared to be at increased risk. Patients having abnormally high ABPI (≥ 1.3) also had poor prognosis (HR, 2.33 [1.11 to 4.89] and 3.04 [1.14 to 8.12] for all-cause and cardiovascular mortality, respectively). Thus, the present findings validate ABPI as a powerful and independent predictor for all-cause and cardiovascular mortality among hemodialysis patients.

Growing numbers of patients are now on hemodialysis as a result of end-stage renal disease (ESRD). ESRD is associated with a substantially reduced life expectancy, of which cardiovascular disease (CVD) is the leading cause (1–3). Several cardiovascular risk factors are applicable to both the general and the hemodialysis population. In contrast, some cardiovascular risk factors are present to a greater extent in the hemodialysis population than in the general population, while others appear irrelevant in hemodialysis patients (4). Therefore, it is important to define risk factors critical for overall and cardiovascular mortality in this patient population. Identification of patients who require aggressive preventive and interventional strategies should ultimately improve their survival and quality of life.

Peripheral arterial occlusive disease (PAOD) has recently attracted much attention as a risk factor for adverse outcomes. Epidemiological and clinical studies of the general population have clearly shown that PAOD is a strong predictor for subsequent cardiovascular and overall mortality (5–8). Limited available data also suggest that PAOD is prevalent in hemodialysis patients (4,9–11) and is associated with poor outcomes (9,10). However, evaluation of PAOD receives relatively little attention among hemodialysis patients. Hence they are less likely to receive appropriate treatment than those, for example, with coronary artery disease.

Ankle-brachial BP index (ABPI; the ratio of ankle to brachial systolic BP) is a simple, non-invasive, and reliable method to access PAOD. Not only useful in diagnosing PAOD, large-scale studies showed that ABPI is a strong predictor for CVD and mortality (5–8). However, the measurement of ABPI has not been fully validated in the ESRD population. Therefore, we sought in the current study to clarify the diagnostic and prognostic value of ABPI in hemodialysis patients. The ABPI was measured at the baseline in a cohort of Japanese patients who require aggressive preventive and interventional
patients undergoing chronic hemodialysis. All subjects had detailed assessment of other risk factors and were followed-up for 2 yr on average. We found that there is a graded inverse relationship between the ABPI and both cardiovascular and all-cause mortality. Multivariate analysis indicated that ABPI is independent from other risk factors, including advanced age, hypertension, and diabetes mellitus. Thus, the measurement of ABPI effectively identifies high-risk hemodialysis patients, a target population requiring intensive follow-up.

Materials and Methods

Study Design and Patients

This prospective cohort study was conducted at 15 dialysis centers in the Gunma and Saitama districts of Japan. To be eligible for this study, patients had to have received regular hemodialysis at least for 3 mo just before entry. Moreover, patients had to be clinically stable for 3 mo before entry and specifically lack acute cardiovascular, cerebrovascular, infectious, or other active diseases. A total of 1010 patients were recruited from November 1999 to July 2001. All of them agreed to participate in the follow-up study. The mean ± SD age of the cohort was 60.6 ± 12.5 yr. The observation ended in May 2002. During the follow-up period, one patient received a renal transplant. This patient was followed until the date of transplantation and then censored. Twenty-eight patients moved away from the study dialysis centers. Among these, outcome data from ten patients could be obtained. The remaining 18 patients were censored at departure to another dialysis unit. The mean patient follow-up was 22.3 ± 5.6 mo.

Demographic and medical data were obtained from medical records and interviews with patients and/or the patient’s primary nephrologists at study entry. These include age, gender, smoking history (ever versus never), body mass index (BMI, weight/height²), comorbid conditions, serum creatinine, albumin, cholesterol, and KT/V. Comorbid conditions were defined as follows. Coronary artery disease: a history of exertional angina, a history of ischemic electrocardiogram change followed by medication of vasodilator, previous angiogram showing significant occlusive disease, a history of a past myocardial infarction, or a history of coronary artery bypass surgery or angioplasty. Cerebrovascular disease: a history of cerebrovascular accident including cerebral bleeding and infarction. Hypertension: systolic BP ≥ 160 mmHg and/or diastolic pressure ≥ 90 mmHg and/or taking anti-hypertensive medication. Diabetes mellitus (DM): the use of insulin or the presence of chronic renal failure due to DM nephropathy at the start of hemodialysis. Blood samples for creatinine, albumin, and cholesterol were obtained at predialysis as a part of routine clinical work within one month of enrollment. KT/V was determined according to the procedure of Shinzato et al. (12).

An age- and gender-matched control group consisted of 299 healthy volunteers, 112 women and 187 men. Mean ± SD age of the control was 59.8 ± 10.2 yr. Criteria for inclusion in the control group included normal renal function, normal pulse rate, no symptoms of claudication, no evidence of ischemic ulcers, gangrene, or amputations of the lower extremity and no previous history of cardiovascular disease. Subjects were excluded from the control group if they had one or more risk factors for vascular disease, including DM (fasting plasma glucose ≥ 140 mg/dl, hypoglycemic medications, or the presence of DM nephropathy), hypertension (systolic BP ≥ 160 mmHg and/or diastolic pressure ≥ 90 mmHg and/or taking anti-hypertensive medication), or hypercholesteremia (fasting cholesterol ≥ 260 mg/dl).

ABPI Measurement

ABPI was determined in all participants and control individuals using ABI-form (Colin, Japan), which simultaneously measures bilateral arm and ankle (brachial and posterior tibial arteries, respectively) BP by an oscillometric method. Before this study, the agreement was assessed between the oscillometric and the conventional Doppler methods in measuring ankle BP in 238 volunteers, including healthy subjects and patients with PAOD (unpublished observations, Mano N., et al.). The variables determined by the two methods were highly correlated with one another (R = 0.985; P < 0.001) even in the range of systolic pressure < 100 mmHg. The mean ± SD of differences was −0.69 ± 6.47 mmHg, and the limits of agreement were 12.2 and −13.6 mmHg, respectively. The BP was measured after completion of the dialysis treatment and after allowing patients at rest in supine position at least for 5 min. Some patients needed more than 15 min for the BP to stabilize. ABPI was calculated by the ratio of the ankle systolic pressure divided by the arm systolic pressure. The systolic pressure of the arm without dialysis access and the lower value of the ankle pressure were used for the calculation. The ABPI measurement was done once in each patient.

Outcome Data Collection

At the end of the follow-up, the status of all patients was assessed and data on mortality were obtained for the entire cohort. We recorded 118 deaths, including 77 fatal cardiovascular events, 36 of which were attributed to heart failure, 14 to cerebral infarction, 11 to the myocardial infarction, 8 to cerebral hemorrhage, 2 to pulmonary embolism, and 2 to ruptured aneurysms. Other cardiovascular events included aortic valve stenosis, ventricular fibrillation, ischemic gangrene of the foot, and sudden cardiac arrest of unknown cause. The 41 fatal noncardiovascular causes were infectious disease (n = 16), cancer (n = 13), gastrointestinal bleeding (n = 3), traffic accident (n = 2), and other (n = 7).

Statistical Analyses

Data are expressed as mean ± SD. The χ² test for trend was used to test for a dose-response relation of variables between ABPI categories. Differences between mean values were assessed by ANOVA. Bivariate associations between the ABPI and discrete variables were evaluated with χ² and unpaired t test in comparison with a group with ABPI ≥1.1 to <1.3. Univariate and multivariate analyses used Cox proportional hazards model. Survival curves were estimated by the Kaplan-Meier method followed by log-rank test. Statistical significance was defined as P < 0.05. All statistical analyses were performed using a computerized statistical package (SPSS for Windows version 10.0, SPSS Inc).

Results

The distribution of measured ABPI in control and hemodialysis subjects is shown in Figure 1. The mean ± SD of ABPI of 229 control subjects was 1.14 ± 0.08. The ABPI of male subjects was significantly higher than that of females (1.15 ± 0.08 versus 1.12 ± 0.08, respectively; P = 0.0047 by unpaired t test). The frequency of subjects with an ABPI < 0.9 was 0.67%, which was equal to that of subjects with an ABPI ≥ 1.3. In contrast, ABPI of hemodialysis patients was distributed more broadly ranging from 0 to 1.75. The frequency distribution of ABPI was 16.5% of patients < 0.9, 8.6% of patients ≥ 0.9 to < 1.0, 16.9% of patients ≥ 1.0 to < 1.1, and 47.0% of patients ≥ 1.1 to < 1.3, whereas 10.9% of patients had an
abnormally high ABPI ($\geq 1.3$). The mean value for the 1010 hemodialysis patients was $1.07 \pm 0.24$, which is significantly lower than that of control subjects ($P < 0.0001$). The difference was also significant between ABPI of male and female hemodialysis patients ($1.08 \pm 0.24$ versus $1.05 \pm 0.23$, respectively; $P = 0.027$ by unpaired t test).

The characteristics of study population at the time of inclusion are shown in Table 1. The age at inclusion was $60.6 \pm 12.5$ yr (range, 18 to 96 yr), and patients were on hemodialysis for $6.5 \pm 5.8$ yr (range, 0.3 to 27.5 yr). Patients were stratified by ABPI into five subgroups ($< 0.9$, $0.9$ to $< 1.0$, $1.0$ to $< 1.1$, $1.1$ to $< 1.3$, and $\geq 1.3$). The characteristics of patients according to stratified ABPI are shown in Table 2. Decreased ABPI level was found to be significantly associated with increased age, prevalence of DM, history of coronary artery disease, history of cerebrovascular disease, increased pulse pressure, decreased diastolic pressure, decreased serum albumin, and decreased creatinine levels ($P < 0.0001$). Smoking history (ever versus never), hypertension, systolic BP, and serum cholesterol levels had no relation to the level of ABPI.

During a 2-yr follow-up, 118 deaths were recorded. Table 3 shows a Cox proportional hazards analysis of the covariates to predict all-cause mortality. In the univariate regression analysis, a hazard ratio (HR) of ABPI $< 0.9$ versus $\geq 1.1$ was 7.09 (95% CI, 2.28 to 11.80). The HR was also significantly increased with even a mild reduction in ABPI (ABPI $< 0.9$ to $< 1.0$, 8.19 [3.64 to 18.44]; ABPI $< 1.0$ to $< 1.1$, 3.65 [1.60 to 8.32]). Moreover, an ABPI $< 1.3$ was also associated with a significant increase in HR ($P = 0.033$), indicating that ABPI $< 1.3$ is another risk factor for mortality. Other predictive variables for mortality included male gender, DM, age, coronary artery disease, cerebrovascular disease, and serum albumin level as variables that independently predicted all-cause mortality. The impact of diabetes mellitus, diastolic BP, and pulse pressure on all-cause mortality was no longer significant.

Seventy-seven cardiovascular deaths were documented during the follow-up period. Table 4 shows a Cox analysis of the ability of various parameters to predict cardiovascular mortality. Crude HR of ABPI $< 0.9$, $0.9$ to $< 1.0$, and $\geq 1.0$ to $< 1.1$ versus ABPI $< 1.1$ was 10.63 [5.24 to 21.58], 8.19 [3.64 to 18.44], and 3.65 [1.60 to 8.32], respectively. Thus, there was an inverse correlation between low ABPI and cardiovascular mortality. Other predictive covariates entering the univariate regression model were age, DM, history of cardiovascular disease, diastolic BP, pulse pressure, albumin level, creatinine level, and serum cholesterol levels ($P < 0.0001$). Multivariate Cox analysis identified the ABPI, age, cardiovascular and coronary artery disease, and serum albumin level as variables that independently predicted all-cause mortality. Other predictive variables for mortality included male gender, DM, age, coronary artery disease, cerebrovascular disease, and serum albumin level as variables that independently predicted all-cause mortality. The impact of diabetes mellitus, diastolic BP, and pulse pressure on all-cause mortality was no longer significant.
artery disease and advanced age. Although DM was a strong predictor in univariate analysis, the statistical impact on cardiovascular mortality was no longer significant in multivariate analysis. Low levels of serum cholesterol paradoxically predicted cardiovascular mortality in univariate and multivariate analyses. A high ABPI (>1.3) was also a significant parameter independently predicting cardiovascular mortality (HR, 3.04 [1.14 to 8.12]).

To further demonstrate the predictive value of a low ABPI, we separately analyzed patients who had no previous cardiovascular events (n = 728). The frequency distribution of ABPI in this subpopulation was 12.5% of patients <0.9, 7.7% of patients ≥0.9 to <1.0, 16.2% of patients 1.0 ≥ to <1.1, and 51.8% of patients ≥1.1 to <1.3, whereas 11.8% of patients had an abnormally high ABPI (≥1.3). As shown in Table 5, a low ABPI still provides a strong predictor for all-cause mortality in this patient population by multivariate analysis.

Figure 2 shows the Kaplan-Meier curves of all-cause and cardiovascular survival as a function of ABPI values. Comparisons between survival curves by log-rank test were highly significant.

Discussion

It has been reported that ABPI is a valuable tool not only for diagnosis of PAOD but also for predicting mortality and morbidity among elderly or hypertensive patients (5,6,8). However, studies in patients with ESRD have been limited thus far. In the current study, we performed a large-scale, prospective analysis of hemodialysis patients. We found that a low ABPI is strongly associated with a past history of atherosclerotic vascular disease and predicts both all-cause and cardiovascular mortality. Multivariate analysis revealed that the role of low ABPI was independent of other risk factors known to affect mortality in hemodialysis patients, namely advanced age, DM, preexisting cardiovascular disease, BP, and serum albumin levels. Although a low ABPI is strongly associated with a history of atherosclerotic vascular disease, its power to predict survival is still remarkable even when patients with no preceding cardiovascular events were analyzed separately.

ABPI was determined using ABI-form (Colin, Japan), which simultaneously measures arm and ankle BP by an oscillometric method. This automatic devise allowed us to measure ABPI quickly, non-invasively, and reproducibly. Previous studies validated the oscillometric method for measuring arterial BP in hemodialysis (13,14) or PAOD patients (15). However, Jonsson et al. (16) recently argued that ankle BP by the oscillometric method tended to record values higher than those measured by the conventional Doppler method. The discrepancy was significant when systolic ankle BP was <100 mmHg. Such overestimation of ankle BP by the oscillometric method might overlook PAOD by overestimating ABPI. However, the ABI-form solves this problem by introducing a double cuff configuration, which is composed of an occlusion cuff and a sensor cuff. As described in Materials and Methods, the agree-

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### Table 2. Characteristics of patients at inclusion according to stratified ankle-brachial BP index (ABPI)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>&lt;0.9 (n = 167)</th>
<th>≥0.9 to &lt;1.0 (n = 87)</th>
<th>≥1.0 to &lt;1.1 (n = 171)</th>
<th>≥1.1 to &lt;1.3 (n = 475)</th>
<th>≥1.3 (n = 110)</th>
<th>P value ANOVA or χ² test (trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.4 ± 10.9a</td>
<td>63.2 ± 12.0d</td>
<td>60.8 ± 12.3</td>
<td>58.9 ± 12.7</td>
<td>58.0 ± 11.9a</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>59.9</td>
<td>57.5</td>
<td>61.4</td>
<td>63.2</td>
<td>78.2a</td>
<td>0.012</td>
</tr>
<tr>
<td>Duration of dialysis (yr)</td>
<td>5.9 ± 4.7</td>
<td>5.9 ± 5.5</td>
<td>7.7 ± 6.6</td>
<td>6.4 ± 5.8</td>
<td>6.2 ± 6.1</td>
<td>0.034</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>61.7b</td>
<td>33.3</td>
<td>31</td>
<td>25.5</td>
<td>31.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking history (%)</td>
<td>49.1</td>
<td>35.6</td>
<td>40.9</td>
<td>40.6</td>
<td>38.2</td>
<td>0.209</td>
</tr>
<tr>
<td>Coronary artery disease (%)</td>
<td>27.5b</td>
<td>27.5b</td>
<td>22.8b</td>
<td>12.6</td>
<td>11.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cerebrovascular disease (%)</td>
<td>25.7b</td>
<td>18.4a</td>
<td>11.1</td>
<td>9.5</td>
<td>10.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>80.8</td>
<td>87.4</td>
<td>77.8</td>
<td>78.9</td>
<td>71.8</td>
<td>0.108</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>143.8 ± 23.4</td>
<td>142.4 ± 27.1</td>
<td>141.6 ± 23.6</td>
<td>141.7 ± 22.0</td>
<td>137.6 ± 20.0</td>
<td>0.279</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77.3 ± 12.7d</td>
<td>77.7 ± 13.9d</td>
<td>80.6 ± 11.9</td>
<td>82.3 ± 12.8</td>
<td>80.4 ± 12.9a</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>66.5 ± 16.2d</td>
<td>64.7 ± 19.8d</td>
<td>61.0 ± 16.9</td>
<td>59.4 ± 15.6</td>
<td>56.9 ± 12.1b</td>
<td>&lt;0.0001</td>
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<tr>
<td>BMI</td>
<td>20.7 ± 3.1</td>
<td>20.2 ± 2.9</td>
<td>20.3 ± 3.6</td>
<td>20.7 ± 2.7</td>
<td>21.5 ± 2.7c</td>
<td>0.016</td>
</tr>
<tr>
<td>Albumin level (g/dl)</td>
<td>3.7 ± 0.4d</td>
<td>3.7 ± 0.4d</td>
<td>3.8 ± 0.4d</td>
<td>3.9 ± 0.4</td>
<td>3.6 ± 0.5a</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol level (mg/dl)</td>
<td>157.7 ± 37.3</td>
<td>154.9 ± 33.2</td>
<td>153.5 ± 30.8</td>
<td>154.4 ± 34.0</td>
<td>149.5 ± 28.8c</td>
<td>0.394</td>
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<tr>
<td>Creatinine level (mg/dl)</td>
<td>9.7 ± 2.8d</td>
<td>10.0 ± 3.1d</td>
<td>10.9 ± 3.0</td>
<td>11.3 ± 3.0</td>
<td>11.1 ± 3.3a</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.21 ± 0.28</td>
<td>1.32 ± 0.29</td>
<td>1.2 ± 0.27</td>
<td>1.26 ± 0.27</td>
<td>1.21 ± 0.27a</td>
<td>0.027</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>30.2 ± 3.9</td>
<td>30.3 ± 3.4</td>
<td>30.8 ± 3.5</td>
<td>30.2 ± 3.4</td>
<td>30.0 ± 3.6a</td>
<td>0.394</td>
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</table>

*p < 0.05, χ² test in comparison with ABPI ≥1.1 to <1.3.

bP < 0.01, χ² test in comparison with ABPI ≥1.1 to <1.3.

P < 0.05, Unpaired t test in comparison with ABPI ≥1.1 to <1.3.

P < 0.01, Unpaired t test in comparison with ABPI ≥1.1 to <1.3.
was used. It should also be stressed that ABPI/Cox proportional hazards regression analysis for all-cause mortality
Table 3. PAOD may be underestimated when the criteria of ABPI/mellitus with possible vascular calcification, the prevalence of extremities (20,21). Because many of our patients had diabetes patients with extensive vascular calcification of the lower obstruction as well. ABPI values can be falsely elevated among rate suggests that a substantial part of this group has arterial calculation (22,23). Thus, hemodialysis patients with a mod-
ABPI values of < 0.9 have been established as a reliable diagnostic marker for PAOD with high sensitivity and specificity (17–19), indicating that at least 16.5% of our studied population had PAOD. However, the fact that patients with ABPI ≥ 0.9 to < 1.0 had a significantly increased mortality rate suggests that a substantial part of this group has arterial obstruction as well. ABPI values can be falsely elevated among patients with extensive vascular calcification of the lower extremities (20,21). Because many of our patients had diabetes mellitus with possible vascular calcification, the prevalence of PAOD may be underestimated when the criteria of ABPI < 0.9 was used. It should also be stressed that ABPI ≥ 1.3 is more prevalent in hemodialysis patients than in control subjects. This abnormally high ABPI has been interpreted as a sign of medial wall calcification (21). Long-term hemodialysis patients have advanced arterial calcification, a process in which abnormal calcium and phosphate metabolism plays a pivotal role. The high prevalence of ABPI ≥ 1.3 in our patient population may reflect such ESRD-related pathologic states. Toe brachial BP index (TBBP) is an alternative method to solve this issue, which overcomes the false elevation of ABPI due to calcification (22,23). Thus, hemodialysis patients with a mod-erate reduction of ABPI (≥ 0.9 to < 1.1) as well as with an abnormally high ABPI should be monitored carefully.
Previous studies identified several risk factors for PAOD among hemodialysis patients, including advanced age, diabetes mellitus, a history of cardiovascular and cerebrovascular diseases, smoking history, low diastolic BP, and low albumin levels (4,24). In the current study, we confirmed most of these. An interesting and novel finding is a strong correlation of low levels (4,24). In the current study, we confirmed most of these. An interesting and novel finding is a strong correlation of low
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate</th>
<th>Multivariate</th>
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<tr>
<td></td>
<td>Hazard Ratios (95% CI)</td>
<td>P Value</td>
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<tr>
<td>ABPI (versus ≥1.1 to 1.3&lt;)</td>
<td></td>
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<tr>
<td>&lt;0.9</td>
<td>7.09 (2.28 to 11.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥0.9 to &lt;1.0</td>
<td>4.83 (2.59 to 9.01)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥1.0 to &lt;1.1</td>
<td>2.43 (1.32 to 4.49)</td>
<td>0.005</td>
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<tr>
<td>≥1.3</td>
<td>2.20 (1.07 to 4.54)</td>
<td>0.033</td>
</tr>
<tr>
<td>Age (per 1yr)</td>
<td>1.06 (1.04 to 1.07)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Male versus female</td>
<td>1.64 (1.09 to 2.48)</td>
<td>0.018</td>
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<tr>
<td>Duration of dialysis (per 1 yr)</td>
<td>0.98 (0.95 to 1.01)</td>
<td>0.272</td>
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<tr>
<td>Diabetes mellitus</td>
<td>1.88 (1.31 to 2.69)</td>
<td>0.001</td>
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<td>Smoking (ever versus never)</td>
<td>1.55 (1.08 to 2.22)</td>
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<td>Coronary artery disease</td>
<td>2.93 (2.02 to 4.26)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Cerebrovascular disease</td>
<td>3.67 (2.50 to 5.37)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Hypertension</td>
<td>0.92 (0.59 to 1.47)</td>
<td>0.692</td>
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<tr>
<td>Systolic BP (per 1 mmHg)</td>
<td>1.01 (0.997 to 1.01)</td>
<td>0.232</td>
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<tr>
<td>Diastolic BP (per 1 mmHg)</td>
<td>0.98 (0.96 to 0.99)</td>
<td>0.002</td>
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<tr>
<td>Pulse pressure (per 1 mmHg)</td>
<td>1.02 (1.01 to 1.03)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.91 (0.86 to 0.98)</td>
<td>0.006</td>
</tr>
<tr>
<td>Creatinine level (per 1 mg/dl)</td>
<td>0.87 (0.82 to 0.92)</td>
<td>&lt;0.0001</td>
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<tr>
<td>Cholesterol level (per 1 mg/dl)</td>
<td>0.99 (0.99 to 1.00)</td>
<td>0.009</td>
</tr>
<tr>
<td>Albumin level (per 1 g/dl)</td>
<td>0.28 (0.19 to 0.43)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>K/U (per 1.0)</td>
<td>0.38 (0.19 to 0.76)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hematocrit (per 1%)</td>
<td>0.98 (0.93 to 1.03)</td>
<td>0.411</td>
</tr>
</tbody>
</table>

In addition to ABPI, we analyzed multiple conventional risk factors for mortality in hemodialysis patients. Although DM was a strong predictor in univariate analysis, there was no statistical significance in multivariate analysis on all-cause and cardiovascular mortality. Thus, the impact of DM might be mediated by atherosclerotic vascular disease represented by a low ABPI. Low levels of serum albumin, serum creatinine, and BMI are parameters indicating malnutrition, and have been repeatedly regarded as powerful predictors for the poor prognosis of hemodialysis patients (27–30). On multivariate analysis, however, low ABPI was a more powerful predictor than these other parameters. As described, a low ABPI was sig-
significantly associated with a past history of cardiovascular atherosclerotic diseases. However, we demonstrated that a low ABPI still provides a strong predictor for all-cause mortality in patients with no preceding cardiovascular events. This further supports the validity of ABPI measurement in hemodialysis patients.

In summary, low ABPI is associated with poor prognosis in Japanese hemodialysis population. The oscillometric method proved to be valuable in screening such high-risk patients. Effective screening will allow us to identify patients who are likely to benefit from close follow-up and multiple interventions, which are of proven value in the general population. Limitations of measuring ABPI in hemodialysis patients were also discussed and should be overcome in the future. Such

### Table 4. Cox proportional hazards regression analysis for cardiovascular mortality

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratios (95% CI)</td>
<td>P Value</td>
<td>Hazard Ratios (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td><strong>ABPI (versus 1.1 to 1.3)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9</td>
<td>10.63 (5.24 to 21.58)</td>
<td>&lt;0.0001</td>
<td>5.90 (2.83 to 12.29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>0.9 to 1.0</td>
<td>10.63 (5.24 to 21.58)</td>
<td>&lt;0.0001</td>
<td>5.90 (2.83 to 12.29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1.0 to 1.1</td>
<td>3.65 (1.60 to 8.32)</td>
<td>0.019</td>
<td>2.82 (1.22 to 6.54)</td>
<td>0.016</td>
</tr>
<tr>
<td>1.3</td>
<td>3.08 (1.17 to 8.09)</td>
<td>0.027</td>
<td>3.04 (1.14 to 8.12)</td>
<td>0.025</td>
</tr>
<tr>
<td><strong>Age (per 1 yr)</strong></td>
<td>1.06 (1.04 to 1.08)</td>
<td>&lt;0.0001</td>
<td>1.04 (1.01 to 1.07)</td>
<td>0.014</td>
</tr>
<tr>
<td><strong>Male versus female</strong></td>
<td>1.46 (0.89 to 2.40)</td>
<td>0.132</td>
<td>1.44 (0.79 to 2.64)</td>
<td>0.239</td>
</tr>
<tr>
<td><strong>Duration of dialysis (per 1 yr)</strong></td>
<td>0.98 (0.95 to 1.02)</td>
<td>0.435</td>
<td>1.02 (0.97 to 1.08)</td>
<td>0.386</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>2.17 (1.38 to 3.39)</td>
<td>0.0007</td>
<td>1.43 (0.84 to 2.42)</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>Smoking (ever versus never)</strong></td>
<td>1.56 (0.998 to 2.44)</td>
<td>0.0512</td>
<td>1.16 (0.69 to 1.93)</td>
<td>0.576</td>
</tr>
<tr>
<td><strong>Coronary artery disease</strong></td>
<td>4.30 (2.75 to 6.74)</td>
<td>&lt;0.0001</td>
<td>2.52 (1.57 to 4.02)</td>
<td>0.0001</td>
</tr>
<tr>
<td><strong>Cerebrovascular disease</strong></td>
<td>3.21 (1.98 to 5.20)</td>
<td>&lt;0.0001</td>
<td>1.85 (1.10 to 3.12)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>0.99 (0.57 to 1.71)</td>
<td>0.965</td>
<td>1.19 (0.64 to 2.21)</td>
<td>0.588</td>
</tr>
<tr>
<td><strong>Systolic BP (per 1 mmHg)</strong></td>
<td>1.00 (0.99 to 1.01)</td>
<td>0.878</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Diastolic BP (per 1 mmHg)</strong></td>
<td>0.97 (0.96 to 0.99)</td>
<td>0.003</td>
<td>0.99 (0.97 to 1.01)</td>
<td>0.512</td>
</tr>
<tr>
<td><strong>Pulse pressure (per 1 mmHg)</strong></td>
<td>1.02 (1.01 to 1.03)</td>
<td>0.008</td>
<td>1.00 (0.99 to 1.02)</td>
<td>0.913</td>
</tr>
<tr>
<td><strong>BMI (per 1 kg/m²)</strong></td>
<td>0.95 (0.87 to 1.02)</td>
<td>0.157</td>
<td>0.97 (0.89 to 1.05)</td>
<td>0.429</td>
</tr>
<tr>
<td><strong>Creatinine level (per 1 mg/dl)</strong></td>
<td>0.86 (0.80 to 0.93)</td>
<td>&lt;0.0001</td>
<td>0.96 (0.87 to 1.06)</td>
<td>0.39</td>
</tr>
<tr>
<td><strong>Cholesterol level (per 1 mg/dl)</strong></td>
<td>0.99 (0.98 to 0.996)</td>
<td>0.003</td>
<td>0.99 (0.98 to 0.998)</td>
<td>0.011</td>
</tr>
<tr>
<td><strong>Albumin level (per 1 g/dl)</strong></td>
<td>0.29 (0.17 to 0.49)</td>
<td>&lt;0.0001</td>
<td>0.54 (0.28 to 0.99)</td>
<td>0.049</td>
</tr>
<tr>
<td><strong>Kt/V (per 1.0)</strong></td>
<td>0.36 (0.15 to 0.83)</td>
<td>0.016</td>
<td>0.51 (0.19 to 1.35)</td>
<td>0.174</td>
</tr>
<tr>
<td><strong>Hematocrit (per 1%)</strong></td>
<td>0.99 (0.94 to 1.07)</td>
<td>0.973</td>
<td>1.04 (0.97 to 1.11)</td>
<td>0.286</td>
</tr>
</tbody>
</table>

### Table 5. Cox proportional hazards analysis for all-cause mortality in patients without previous cardiovascular disease at baseline

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Univariate</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratios (95% CI)</td>
<td>P Value</td>
<td>Hazard Ratios (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td><strong>ABPI (versus 1.1 to 1.3)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.9</td>
<td>5.48 (2.57 to 11.71)</td>
<td>&lt;0.0001</td>
<td>3.02 (1.35 to 6.76)</td>
<td>0.009</td>
</tr>
<tr>
<td>0.9 to 1.0</td>
<td>4.69 (1.92 to 11.47)</td>
<td>0.0007</td>
<td>4.04 (1.61 to 10.16)</td>
<td>0.003</td>
</tr>
<tr>
<td>1.0 to 1.1</td>
<td>1.82 (0.73 to 4.73)</td>
<td>0.19</td>
<td>1.65 (0.65 to 4.21)</td>
<td>0.297</td>
</tr>
<tr>
<td>1.3</td>
<td>2.24 (0.84 to 5.96)</td>
<td>0.11</td>
<td>2.09 (0.77 to 5.64)</td>
<td>0.146</td>
</tr>
<tr>
<td><strong>Age (per 1 yr)</strong></td>
<td>1.06 (1.04 to 1.09)</td>
<td>&lt;0.0001</td>
<td>1.04 (1.01 to 1.08)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Male versus female</strong></td>
<td>1.63 (0.86 to 3.01)</td>
<td>0.13</td>
<td>2.04 (1.03 to 4.02)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>Diabetes mellitus</strong></td>
<td>2.08 (1.18 to 3.66)</td>
<td>0.0115</td>
<td>1.42 (0.64 to 2.32)</td>
<td>0.548</td>
</tr>
<tr>
<td><strong>Diastolic BP (per 1 mmHg)</strong></td>
<td>0.98 (0.98 to 0.99)</td>
<td>0.0344</td>
<td>0.99 (0.96 to 1.01)</td>
<td>0.276</td>
</tr>
<tr>
<td><strong>Pulse pressure (per 1 mmHg)</strong></td>
<td>1.03 (1.01 to 1.04)</td>
<td>0.0013</td>
<td>1.02 (1.00 to 1.04)</td>
<td>0.123</td>
</tr>
<tr>
<td><strong>Creatinine level (per 1 mg/dl)</strong></td>
<td>0.84 (0.76 to 0.92)</td>
<td>0.0002</td>
<td>0.95 (0.85 to 1.07)</td>
<td>0.403</td>
</tr>
<tr>
<td><strong>Albumin level (per 1 g/dl)</strong></td>
<td>0.21 (0.11 to 0.39)</td>
<td>&lt;0.0001</td>
<td>0.26 (0.12 to 0.55)</td>
<td>0.0015</td>
</tr>
</tbody>
</table>
efforts might help ultimately improve survival and quality of life in hemodialysis patients.

Acknowledgments

The nursing and technical staffs of the 15 dialysis units, who helped to collect the clinical data, are gratefully acknowledged for their assistance. We thank Nobue Mano (First Department of Surgery, Nagoya University) for measuring ABPI by Doppler method in comparison with oscillometric method. We also thank Kenji Kawachi (Kawachi Cardiovascular Clinic), Hisao Kumakura (Cardiovascular Clinic), Hidaka Hospital, and David Rothstein (Yale University, New Haven, CT) for their helpful suggestions.

Appendix: the Gunma Dialysis and ASO Study Group Members

Fujioka General Hospital: K. Fukasawa; Toho Hospital: Y. Abe, K. Amemiya, K. Kaji, S. Tokisawa; Usui Hospital: H. Koyanagi, M. Kobayashi; Fukaya Red Cross Hospital: Y. Ishii, T. Yamamoto, M. Sakai; Zen-shukai Hospital: J. Hayashi; Shibukawa Central Hospital: M. Shinohara, Y. Yamada; Mae-bashi Saiseikai Hospital: C. Takagi, Y. Shimizu, T. Kitahara; Komoro Kosei Hospital: T. Noguchi, M. Yamashita; Watanabe Clinic: Y. Watanabe; Tone Central Hospital: A. Nada, S. Kobayashi; Shimada Memorial Hospital: H. Kanai; Shirane Clinic: T. Sekihara; Nishikatakai Clinic: T. Matsumoto; Hidaka Hospital: H. Ishida.

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