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Original article

Development and validation of optimal cut-off value in inter-arm systolic blood pressure difference for prediction of cardiovascular events

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ABSTRACT

Background: An inter-arm systolic blood pressure difference (IAD) is associated with cardiovascular disease. The aim of this study was to develop and validate the optimal cut-off value of IAD as a predictor of major adverse cardiac events in patients with arteriosclerosis risk factors.

Methods: From 2009 to 2014, 1076 patients who had at least one cardiovascular risk factor were included in the analysis. We defined 700 randomly selected patients as a development cohort to confirm that IAD was the predictor of cardiovascular events and to determine optimal cut-off value of IAD. Next, we validated outcomes in the remaining 376 patients as a validation cohort. The blood pressure (BP) of both arms measurements were done simultaneously using the ankle-brachial blood pressure index (ABI) form of automatic device. The primary endpoint was the cardiovascular event and secondary endpoint was the all-cause mortality.

Results: During a median period of 2.8 years, 143 patients reached the primary endpoint in the development cohort. In the multivariate Cox proportional hazards analysis, IAD was the strong predictor of cardiovascular events (hazard ratio: 1.03, 95% confidence interval: 1.01–1.05, $p = 0.005$). The receiver operating characteristic curve revealed that 5 mmHg was the optimal cut-off point of IAD to predict cardiovascular events ($p < 0.001$). In the validation cohort, the presence of a large IAD (IAD $\geq$5 mmHg) was significantly associated with the primary endpoint ($p = 0.021$).

Conclusions: IAD is significantly associated with future cardiovascular events in patients with arteriosclerosis risk factors. The optimal cut-off value of IAD is 5 mmHg.

Introduction

Cardiovascular disease is a major health problem, accounting for 30% of all deaths in Asian countries [1]. This disease is a health problem that demands a clinical approach to prevention, early detection, and monitoring of the progression of the disease. Arteriosclerosis is a major contributor to the development of cardiovascular disease and is a major cause of mortality and morbidity [2,3]. Measurement of blood pressure (BP) is the most frequently and simplest method to assess the activity of arteriosclerosis [4]. In the clinical setting, cases with a difference of BP were found occasionally [5,6]. Meta-analyses reported that a difference in systolic BP of 10 mmHg or more between both arms was associated with development of cardiovascular events [7–9]. However, the cut-off value of 10 mmHg or 15 mmHg seems to be an equivocal index because of limited evidence [10]. The optimal cut-off value of inter-arm systolic blood pressure

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difference (IAD) is needed and should be tested to predict cardiac events. The aim of this study was to develop and validate the optimal cut-off value of IAD as a predictor of major adverse cardiovascular events in patients with arteriosclerosis risk factors.

Methods

Study design and data collection

This was a single center prospective observational study. A total of 1160 patients consulted Tokushima Prefectural Miyoshi Hospital, from April 2009 to December 2014, who received a medical service under health insurance. We included patients with at least one or more arteriosclerotic risk factors. Risk factors were diabetes mellitus, hypertension, dyslipidemia, smoking history, history of coronary artery disease, history of cerebrovascular disease, or history of peripheral arterial disease [11]. The exclusion criteria were inability to measure BP in both arms (e.g. deficiency or shunt), death within 1 month, or inability to keep track of or participate in follow-up. After the exclusions, 1076 patients were included for the analysis. There were no missing data during follow-up. This was a development and validation study. An independent data set was used to develop the model. Because of the necessity of large number of development cohort, we defined 700 randomly selected patients using a statistical software (SPSS for Windows version 22.0; SPSS Inc., Chicago, IL, USA) as a development cohort to confirm that IAD was the predictor of cardiovascular events and to determine optimal cut-off value of IAD. Next, we validated outcomes in the remaining 376 patients as a validation cohort [12,13]. The Institutional Review Board of the Tokushima University Hospital approved the study protocol.

Blood pressure measurements

The BP measurements of both arms were done simultaneously using the ankle-brachial BP index (ABI) form of automatic device (Omron Healthcare, Kyoto, Japan) [14,15]. Measurements were taken in the sequence of right arm, left arm, right ankle, and left ankle and repeated twice in the supine position with appropriately sized cuffs. First measurement is performed to estimate BP roughly and synchronizes a phase at the pressurization of the cuffs, and second measurement is performed subsequently for the actual value. Therefore, this method has fewer random variations than a method using two sphygmomanometers. The IAD was defined as the absolute difference of systolic BP of both arms. The maximal difference between arms was used. The ABI and brachial-ankle pulse wave velocity (baPWV) were measured after a 15-min rest period in the supine position in an air-conditioned room using a vascular testing device [16]. The ABI was calculated separately for each leg, and the lower of the 2 ABI values was used for analysis and the higher of the 2baPWV values was used for the analysis [17].

Clinical outcomes

The endpoints were obtained by reviewing all medical records including the last hospitalization, nursing home records, and personal physical records. Based on past studies, the primary endpoint was cardiovascular event defined as new onset of acute myocardial infarction, angina, coronary restenosis, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack, or peripheral arterial disease [18,19]. Each diagnosis was based on a coronary angiography, coronary computed tomography (CT), magnetic resonance imaging of the brain, head CT or contrast vascular CT. The second endpoint was all-cause mortality. The duration of follow-up began at the time of the initial tests and ended in March 2016.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 22.0; SPSS Inc., Chicago, IL, USA) [20]. Multiple logistic regression analysis for Cox proportional hazards models was used to predict a factor of cardiovascular events and all-cause mortality. Significant variables in univariate analysis ($p < 0.05$) were selected as the covariates for multivariate analysis for Cox proportional hazards models. A receiver operating characteristic curve (ROC) was constructed on the basis of the sensitivity and specificity of the predictions for cardiovascular events from the development cohort. We determined the optimal cut-off value using Youden index [21]. This optimal cut-off value was used to validate the prediction of cardiovascular events. We divided a validation cohort into two groups with the optimal cut-off value of IAD. An event-free curve was estimated using the Kaplan–Meier method. The log-rank test was used to compare the differences in event-free rates between two groups. The differences between groups were checked by Chi-square test for categorical variables or by independent t test for continuous variables. To assess the reproducibility of BP differences between arms, the second measurements of BP using ABI-form was done in 50 randomly selected patients. To evaluate the measurement accuracy about this cut-off value, we used Pearson's correlation test. A value of $p < 0.05$ was considered statistically significant.

Results

Patient characteristics

One thousand and seventy six patients were enrolled in this study. The purposes of measurement were a screening examination for arteriosclerotic disease ($n = 770$, 71.6%) and to rule out peripheral arterial disease ($n = 306$, 28.4%). Patients in the development cohort ($n = 700$) had a mean age of 72 years, 48% were female. The comorbidities in this cohort were 69% of patients with hypertension, 30% of patients had diabetes mellitus, 20% were smokers, and 42% had dyslipidemia. Median IAD was 4 mmHg. In the BP examination, 506 patients (72%) had no difference, less than 5 mmHg. Eighty-one patients (11%) were lower in the right arm, and 113 patients (16%) were lower with the left arm. All patients in the development cohort were followed for an average of 2.8 ± 1.6 years. Patients in the validation cohort ($n = 376$) had a mean age of 73 years, 42% were female. All patients in the validation cohort were also followed for an average of 2.8 ± 1.6 years. We show patient characteristics that compared the development cohort with the validation cohort in Table 1. No significant differences were observed with regard to clinical background between the two groups.

Development cohort

In the development cohort, 143 (20%) patients reached the primary endpoint (cardiovascular events), and 78 (11%) patients reached the secondary endpoint (all-cause death). The causes of cardiovascular events were defined as new onset of acute myocardial infarction ($n = 4$, 3%), angina ($n = 33$, 23%), coronary restenosis ($n = 2$, 1%), cerebral infarction ($n = 27$, 19%), cerebral hemorrhage ($n = 6$, 4%), subarachnoid hemorrhage ($n = 4$, 3%), transient ischemic attack ($n = 6$, 4%) and peripheral arterial disease ($n = 40$, 28%).

In univariate analysis for Cox proportional hazards models, age, IAD, diabetes mellitus, hypertension, smoking, ABI, baPWV, hemoglobin, serum creatinine, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, hemoglobin A1c, brain natriuretic peptide, diuretic, statin, and anti-platelet were

Table 1
Clinical characteristics in development and validation cohort.

	Development cohort	Validation cohort	*p*-Value
Number	700	376	–
Age, years	72 ± 12	73 ± 11	0.324
Male gender (%)	362 (52)	217 (58)	0.06
Body mass index	23 ± 4	23 ± 4	0.753
Systolic BP, mmHg	131 ± 19	132 ± 22	0.641
Diastolic BP, mmHg	75 ± 11	75 ± 13	0.631
IAD, mmHg	4 ± 5	4 ± 4	0.925
Diabetes, *n* (%)	212 (30)	108 (29)	0.593
Hypertension, *n* (%)	480 (69)	269 (72)	0.312
Dyslipidemia, *n* (%)	295 (42)	138 (37)	0.083
Smoking, *n* (%)	140 (20)	89 (24)	0.161
Vascular function tests			
ABI	1.09 ± 0.16	1.07 ± 0.17	0.053
baPWV, cm/s	1928 ± 567	1951 ± 788	0.614
Laboratory data			
Hemoglobin, g/dl	13.4 ± 1.8	13.4 ± 2.0	0.849
Serum creatinine, mg/dl	0.94 ± 0.79	0.94 ± 0.43	0.925
LDL-C, mg/dl	107 ± 34	103 ± 32	0.174
HDL-C, mg/dl	57 ± 16	57 ± 16	0.604
Triglyceride, mg/dl	132 ± 96	126 ± 76	0.303
Hemoglobin A1c, %	6.2 ± 1.3	6.1 ± 1.2	0.229
BNP, pg/dl	112 ± 250	113 ± 223	0.914
Medication			
ARB/ACE-I, *n* (%)	316 (45)	187 (50)	0.150
β-Blocker, *n* (%)	138 (20)	77 (21)	0.765
CCB, *n* (%)	348 (50)	196 (52)	0.450
Diuretic, *n* (%)	158 (23)	96 (26)	0.276
Statin, *n* (%)	263 (38)	144 (38)	0.815
Anti-platelet, *n* (%)	337 (48)	197 (52)	0.184
Warfarin, *n* (%)	57 (8)	40 (11)	0.173

Data are presented as number of patients (percentage) or mean ± SD.
BP, blood pressure; IAD, inter-arm systolic blood pressure difference; ABI, ankle-brachial blood pressure index; baPWV, brachial-ankle pulse wave velocity; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, brain natriuretic peptide; ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

associated with cardiovascular events (Table 2). In the multivariate Cox proportional hazards analysis with stepwise forward regressions, seven factors were selected in the final model and IAD was the strong predictor of cardiovascular events (hazard ratio: 1.03, 95% confidence interval: 1.01–1.05, $p = 0.005$, Table 3). Diabetes did not remain probably in the multivariate analysis for clinical events because glycemic control was good (hemoglobin A1c: 6.2 ± 1.3%) [22]. Interestingly, in univariate analysis for Cox proportional hazards models, IAD was not associated with all-cause mortality (Table 3). Fig. 1 shows the ROC curve to obtain the cut-off value of IAD for cardiovascular events from the development cohort. This ROC curve revealed that 5 mmHg was the optimal cut-off point of IAD (area under the curve: 0.598, 95% confidence interval: 0.543–0.652, $p < 0.001$, Fig. 1). In the development cohort, IAD 5 mmHg or more was found in 81 patients in right arms (42%) and 114 patients in left arms (58%). However, there were no significant differences with arms laterality of IAD in the cardiovascular events ($p = 0.17$) and all-cause mortality ($p = 0.79$). Thus, the arms laterality of IAD was not important to predict cardiovascular event and the absolute value of IAD itself was associated with cardiovascular events.

Reproducibility about cut-off value of IAD

In the 50 randomly selected patients, the correlation between 1st and 2nd measurements of IAD was good ($R = 0.75$, $p < 0.001$, Supplement 1A). Importantly, 46 patients (92%) had IAD differences between 1st and 2nd measurements within 4 mmHg. Only two patients (red lines in Supplement 1B) with low IAD (<5 mmHg) at 1st measurement had high IAD at 2nd measurement (≥5 mmHg) and two patients with high IAD at 1st measurement had low IAD at 2nd measurement (blue lines in Supplement 1B).

Validation cohort with event-free survival

In the validation cohort, 78 (21%) patients reached the primary endpoint (cardiovascular events), and 40 (11%) patients reached the secondary endpoint (all-cause death). In the validation cohort, we conducted the multivariate Cox proportional hazards analysis for the prediction of cardiovascular events and all-cause mortality, shown in Table 4. The IAD was shown to be the predictor of cardiovascular events; hazard ratio of cardiovascular events was 1.04 (95% confidence interval; 1.01–1.07, $p = 0.016$). However, the IAD was not associated with the all-cause mortality. The cut-off value obtained from ROC curve was the same: 5 mmHg (area under the curve: 0.591, 95% confidence interval: 0.520–0.663, $p = 0.013$). We divided a validation cohort into two groups of a large IAD group (Group L: IAD ≥5 mmHg) and small IAD group (Group S: IAD < 5 mmHg). There were no differences in clinical characteristics including antihypertensive therapy between two groups (Table 5). Fig. 2A illustrates the event-free survival of cardiovascular events compared Group L with Group S. Group L had significantly shorter event-free survival of cardiovascular events than Group S in a statistical significance ($p = 0.02$). On the other hand, there were no significant differences in event-free survival curves of all-cause mortality (Fig. 2B, $p = 0.781$).

Discussion

Our development and validation cohort data showed that the IAD was a significant independent predictor of cardiovascular events in patients with risks of cardiovascular disease. An IAD ≥5 mmHg was associated with cardiovascular events in both cohorts. This result suggested that IAD plays an important role for the outcome of this high-risk cohort in daily clinical practice.

Prevalence of IAD

The prevention of major cardiovascular and cerebrovascular events remains a serious public health problem. The IAD is expected to be a simple, easy, and economical parameter that can be measured with no additional equipment to screen patients for cardiovascular disease [23]. The IAD is regularly found in clinical practice. From community based studies, IAD ≥10 mmHg are seen in 5.8–9.2% of people with hypertension [6]. This report of prevalence of IAD is consistent with our results. Our study reported that there were 314 patients (29%) who had a BP difference of 5 mmHg or more, and only 62 patients (6%) who had a BP difference of 10 mmHg or more. This finding emphasized the importance of finding the IAD in clinical practice, because many cases (29%) had IAD of 5 mmHg in patients with risks of cardiovascular disease in the Japanese cohort.

Measurement of IAD

Measurement of BP in both arms is important. However, in the guidelines of the Japanese Hypertensive Society, there were a few mentions for measuring the IAD [4]. In the clinical setting, simultaneous measurements of BP using an automatic device were possible, and manual measurement of BP is subject to bias of interpretation among observers [24,25]. BP data obtained during ABI examination may provide more consistent data for use of IAD. ABI is a widely used clinical test for the assessment of peripheral arterial disease and is an indicator of generalized atherosclerosis [22–24]. IAD had also a prognostic value independent of ABI from our multivariate Cox proportional hazards models. Our findings

Table 2
Univariable association of primary and secondary outcomes in development cohort.

	Primary endpoint		Secondary endpoint	
	Hazard ratio (95% confidence interval)	*p*-Value	Hazard ratio (95% confidence interval)	*p*-Value
Age	1.02 (1.01–1.04)	0.009	1.09 (1.06–1.12)	<0.001
Male gender	1.27 (0.91–1.77)	0.157	1.13 (0.72–1.76)	0.601
Body mass index	0.98 (0.94–1.03)	0.391	0.88 (0.82–0.94)	<0.001
Systolic BP	1.01 (1.00–1.02)	0.143	0.99 (0.98–1.00)	0.153
Diastolic BP	1.01 (1.00–1.03)	0.185	0.99 (0.97–1.01)	0.208
IAD	1.05 (1.03–1.07)	<0.001	1.00 (0.95–1.04)	0.909
Diabetes	0.49 (0.35–0.68)	<0.001	0.91 (0.57–1.46)	0.697
Hypertension	0.66 (0.45–0.98)	0.04	1.10 (0.68–1.77)	0.714
Dyslipidemia	0.99 (0.71–1.38)	0.961	2.35 (1.40–3.93)	0.001
Smoking	0.68 (0.46–0.99)	0.045	0.57 (0.35–0.92)	0.022
Vascular function tests				
ABI	0.14 (0.07–0.31)	<0.001	0.10 (0.04–0.25)	<0.001
baPWV	1.01 (1.00–1.01)	<0.001	1.01 (1.00–1.01)	<0.001
Laboratory data				
Hemoglobin	0.88 (0.81–0.97)	0.009	0.71 (0.63–0.80)	<0.001
Serum creatinine	1.20 (1.09–1.33)	<0.001	1.16 (1.03–1.32)	0.016
LDL-C	0.99 (0.99–1.00)	0.027	0.99 (0.98–1.00)	0.012
HDL-C	0.98 (0.97–0.99)	<0.001	0.99 (0.97–1.00)	0.107
Triglyceride	1.00 (1.00–1.00)	0.53	1.00 (0.99–1.00)	0.249
Hemoglobin A1c	1.11 (1.01–1.22)	0.027	0.82 (0.65–1.04)	0.105
BNP	1.01 (1.00–1.01)	<0.001	1.01 (1.00–1.01)	<0.001
Medication				
ARB/ACE-I	0.87 (0.63–1.21)	0.397	1.34 (0.85–2.10)	0.206
β-Blocker	0.78 (0.53–1.15)	0.213	0.59 (0.36–0.95)	0.029
CCB	1.07 (0.77–1.48)	0.7	1.48 (0.94–2.33)	0.089
Diuretic	0.50 (0.36–0.71)	<0.001	0.27 (0.17–0.42)	<0.001
Statin	0.66 (0.47–0.91)	0.012	1.44 (0.89–2.31)	0.137
Anti-platelet	0.35 (0.24–0.50)	<0.001	0.67 (0.42–1.05)	0.081
Warfarin	0.71 (0.42–1.20)	0.201	0.28 (0.17–0.47)	<0.001

BP, blood pressure; IAD, inter-arm systolic blood pressure difference; ABI, ankle-brachial blood pressure index; baPWV, brachial-ankle pulse wave velocity; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, brain natriuretic peptide; ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

emphasized that physicians should be careful of the presence of a large IAD when assessing an ABI examination.

Prediction for cardiovascular events

Several papers showed that IAD were associated with elevated cardiovascular event rates [25–27]. Evidence for this association is derived from a number of cohort studies and the meta-analysis confirmed these results. However, the relevant cut-off value of IAD on long-term clinical outcomes has not been sufficiently evaluated. Previous papers suggested that 10 mmHg or 15 mmHg is a good cut-off value to predict cardiovascular events [26]. However, there were very few cases with the difference in BP of 10 mmHg in routine practice, and a clinically optimal cut-off value would be needed. The ROC curve in our study revealed that 5 mmHg was the best cut-off points of IAD to predict cardiovascular events. However, 5 mmHg was a small different systolic BP of both arms. Therefore we evaluated the reproducibility of IAD. In our study, the correlation between 1st and 2nd measurements of IAD was good, furthermore IAD of many patients showed less than 5 mmHg (72%). According to these results, this cut-off value of IAD (5 mmHg) was not random variation, and acceptable to assess the prognosis in the clinical setting [27,28]. In the present study, the sample size was relatively large. Also, unlike previous studies, the analysis including the development and validation cohort confirmed the cut-off value of IAD [29].

Table 3
Multi-variable associations of primary and secondary outcomes in development cohort.

	Primary endpoint		Secondary endpoint	
	Hazard ratio (95% confidence interval)	*p*-Value	Hazard ratio (95% confidence interval)	*p*-Value
Age			1.05 (1.01–1.08)	0.005
IAD	1.03 (1.01–1.05)	0.005		
ABI	0.29 (0.12–0.72)	0.007	0.22 (0.08–0.64)	0.006
baPWV	1.01 (1.00–1.01)	<0.001		
Hemoglobin			0.80 (0.69–0.92)	0.002
HDL-C	0.97 (0.96–0.99)	<0.001		
Hemoglobin A1c	1.13 (1.02–1.26)	0.018		
BNP	1.01 (1.00–1.01)	<0.001	1.01 (1.00–1.01)	0.002
Diuretic use			0.55 (0.33–0.90)	0.018
Anti-platelet use	0.43 (0.29–0.65)	<0.001		
Warfarin use			0.50 (0.28–0.88)	0.016

IAD, inter-arm systolic blood pressure difference; ABI, ankle-brachial blood pressure index; baPWV, brachial-ankle pulse wave velocity; HDL-C, high-density lipoprotein cholesterol; BNP, brain natriuretic peptide.

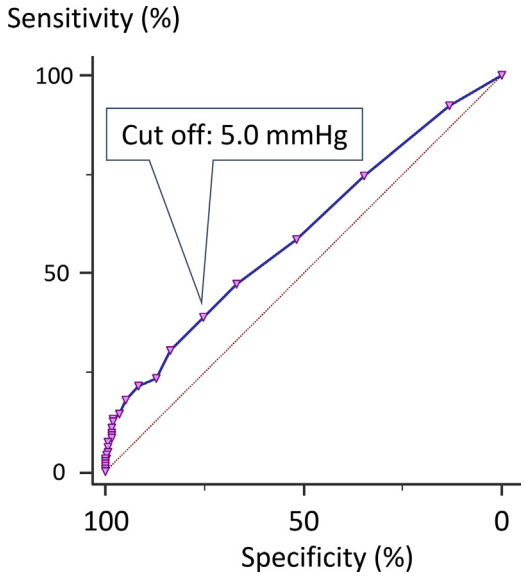

Fig. 1. Receiver operating characteristic curve of inter-arm systolic blood pressure difference for incidence of cardiovascular events in the development cohort.

Explanation for the association between IAD and cardiac events

There are some possible explanations for the significant association between IAD and increased cardiovascular events. Hypertensive patients with a large IAD may be misdiagnosed as normal or controlled BP, because of incorrectly measured BP [5,30]. In addition, one previous study showed that IAD was associated with increased aortic stiffness and left ventricular hypertrophy [31]. This result suggested that a large IAD might be associated with peripheral arterial disease and contribute to the poor prognosis. On the other hand, a large IAD was not associated with all-cause mortality in our cohort. Some possible explanations for this discrepancy include many causes of death in the Japanese population. In addition, one possible explanation was the influence of medications. Our patients had several medications including beta-blocker, statin, or antiplatelet drugs. The use of these medications might influence the association between IAD and all-cause mortality. Further studies to assess the effect of medications for the all-cause mortality should be needed. The IAD is a simple marker, and it is suitable for detection of occult atherosclerosis, but it may not be useful to detect other causes of death (e.g. cancer or infection).

Clinical implications

To the best of our knowledge, this is one of the largest studies evaluating the prognostic utility of IAD in the Japanese population.

Table 5
Comparison of patient characteristics between two groups with IAD in validation cohort.

	Group S: IAD <5 mmHg	Group L: IAD ≥5 mmHg	*p*-Value
Number	256	120	–
Age, years	73 ± 11	72 ± 12	0.494
Male gender (%)	150 (59)	67 (56)	0.614
Body mass index	23 ± 4	24 ± 4	0.067
Systolic BP, mmHg	131 ± 21	134 ± 22	0.084
Diastolic BP, mmHg	75 ± 13	76 ± 13	0.929
IAD, mmHg	2 ± 1	8 ± 5	<0.001
Diabetes, *n* (%)	64 (25)	44 (37)	0.02
Hypertension, *n* (%)	179 (70)	90 (75)	0.309
Dyslipidemia, *n* (%)	85 (33)	53 (44)	0.04
Smoking, *n* (%)	65 (25)	24 (20)	0.252
Vascular function tests			
ABI	1.07 ± 0.16	1.05 ± 0.20	0.257
baPWV, cm/s	1897 ± 688	2065 ± 961	0.055
Laboratory data			
Hemoglobin, g/dl	13.3 ± 2.0	13.4 ± 1.9	0.332
Serum creatinine, mg/dl	0.94 ± 0.41	0.95 ± 0.48	0.762
LDL-C, mg/dl	103 ± 33	102 ± 30	0.801
HDL-C, mg/dl	57 ± 16	57 ± 17	0.920
Triglyceride, mg/dl	124 ± 78	131 ± 70	0.443
Hemoglobin A1c, %	6.0 ± 1.1	6.3 ± 1.3	0.076
BNP, pg/dl	112 ± 190	116 ± 284	0.884
Medication			
ARB/ACE-I, *n* (%)	127 (50)	60 (50)	0.944
β-Blocker, *n* (%)	48 (19)	29 (24)	0.225
CCB, *n* (%)	129 (50)	67 (56)	0.325
Diuretic, *n* (%)	67 (26)	29 (24)	0.678
Statin, *n* (%)	96 (38)	48 (40)	0.642
Anti-platelet, *n* (%)	130 (51)	67 (56)	0.361
Warfarin, *n* (%)	31 (12)	9 (8)	0.177

BP, blood pressure; IAD, inter-arm systolic blood pressure difference; ABI, ankle-brachial blood pressure index; baPWV, brachial-ankle pulse wave velocity; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; BNP, brain natriuretic peptide; ARB, angiotensin II receptor blocker; ACE-I, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker.

This result suggested that a certain threshold of IAD (5 mmHg) was important in prognosis. The inter-arm difference of BP is a simple, reproducible, and inexpensive method for stratifying this high-risk group with cardiovascular disease. However, this cut-off value should be tested on an international large cohort of patients with high risk for cardiovascular disease to predict cardiac events.

Study limitations

There were several limitations to this study. Due to the fact that we enrolled only patients with cardiovascular risks, the results of the present study may not be extrapolated to the general population and should be applied to specific subjects with lifestyle-related diseases. Additionally, because the aim of this prospective study

Table 4
Multi-variable associations of primary and secondary endpoint in validation cohort.

	Primary endpoint		Secondary endpoint	
	Hazard ratio (95% confidence interval)	*p*-Value	Hazard ratio (95% confidence interval)	*p*-Value
Age			1.08 (1.03–1.13)	0.001
IAD	1.03 (1.01–1.07)	0.043		
ABI	0.18 (0.07–0.47)	<0.001		
BNP			1.01 (1.00–1.01)	0.02
Diuretic use			0.39 (0.20–0.76)	0.006
Anti-platelet use	0.47 (0.28–0.81)	0.006		

IAD, inter-arm systolic blood pressure difference; ABI, ankle-brachial blood pressure index; BNP, brain natriuretic peptide.

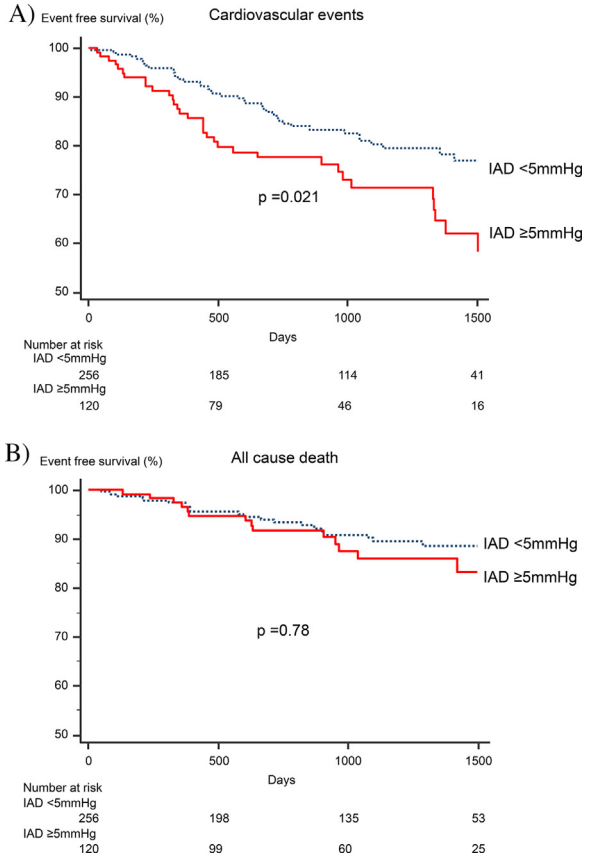

Fig. 2. Kaplan–Meier analysis for cardiovascular events (A) and all-cause death (B) in the validation cohort. Patients with higher IAD (cut-off value: 5 mmHg) had a significantly higher incidence of cardiovascular events. IAD, inter-arm systolic blood pressure difference.

was to assess the utility of the inter-arm difference of BP, other assessments for cardiovascular risks (e.g. carotid ultrasound) were not enrolled in the study from the beginning.

Conclusions

IAD is significantly associated with future cardiovascular events in high-risk patients with cardiovascular disease. The optimal cut-off value of IAD is 5 mmHg from our development and validation cohorts.

Conflict of interest

The authors have no conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jjcc.2017.06.010.

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