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Relationships Between Arterial Pressure-Volume Index and Cardiovascular Disease Biomarkers in Patients With Hypertension

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Abstract

Background: The arterial pressure-volume index (API), which is obtained by conventional blood pressure measurement, is a new marker for arterial stiffness. The aim of this study was to clarify the relationships between the API and various clinical parameters, including cardiovascular disease (CVD) biomarkers, in patients with hypertension for the prevention of CVD.

Methods: This cross-sectional study enrolled 288 patients with hypertension receiving pharmacological treatment, without a history of CVD (males/females: 115/173; age: 63 ± 11 years (mean $\pm$ standard deviation)). The API was automatically calculated using a commercial device.

Results: The API was significantly correlated with important CVD biomarkers, such as the concentration of urinary albumin ($r = 0.42$, $P < 0.001$), high-sensitivity troponin T ($r = 0.39$, $P < 0.001$), and skin autofluorescence (marker of advanced glycation end products in tissues) ($r = 0.41$, $P < 0.001$). Multiple regression analyses demonstrated that when the API was used as a subordinate factor, these biomarkers were independent variables. According to the receiver operating characteristic curve analysis, an API of > 26 is the optimal cut-off point for determining albuminuria as ≥ 30 mg/g Cr, high high-sensitivity cardiac troponin T concentration as ≥ 0.014 ng/mL, or high skin autofluorescence as ≥ 3.0 arbitrary unit (area under the curve = 0.703, 0.702, and 0.704; and $P < 0.001$, respectively).

Conclusion: This investigation demonstrates that API had an independent relationship with relevant CVD biomarkers, such as urinary albumin, high-sensitivity troponin T, and skin autofluorescence. Additionally, the outcomes of receiver operating characteristic curve analysis are presented as values that an API > 26 defines for these biomarkers linked with the formation of CVD.

Keywords: Arterial stiffness; Arterial pressure-volume index; Hypertension; Biomarker; Urinary albumin; High-sensitivity cardiac troponin T; Skin autofluorescence

Introduction

Reduction of blood pressure is an important therapeutic strategy for preventing cardiovascular disease (CVD) events in patients with hypertension [1, 2]. However, patients with CVD events exist despite receiving anti-hypertensive pharmacological treatment. Therefore, we should also consider other factors that may affect the levels of blood pressure during the treatment of hypertension for the prevention of CVD. In fact, several biomarkers detected in blood or urine samples have been investigated and used to prevent CVD events in patients with hypertension [3-5]. Furthermore, researchers have reported that skin autofluorescence (AF), indicating the presence of advanced glycation end products (AGEs) *in vivo*, is a considerable risk factor for CVD in patients with hypertension [6-8]. Arterial stiffness is involved in the pathogenesis of CVD. Several physiological markers of arterial stiffness (e.g., stiffness β, pulse wave velocity, and cardio-ankle vascular index) have been used in clinical settings. A number of clinical reports have shown the usefulness of these physiological markers as risk factors of CVD in patients with hypertension [9-11]. Recently, researchers also investigated a method for calculating the arterial pressure-volume index (API), which indicates arterial stiffness, using oscillometric blood pressure measurements [12]. The API can be easily and immediately obtained by conventional blood pressure measurement in the sitting position. Several studies demonstrated the importance of the API as a risk factor for CVD in the clinical setting [13-15]. Nevertheless, the usefulness of API as a risk factor for CVD in patients with hypertension is currently poorly understood. This cross-sectional investigation ascertained the link between API and various biomarkers of CVD in patients with hypertension. Additionally, using receiver operating characteristic (ROC) curve analysis, this research evaluated the cut-off values of the API for strange levels of CVD biomarkers.

Materials and Methods

Patients

Eligible patients with hypertension were enrolled in this study from September 2019 to August 2020. Patients without history of CVD (e.g., coronary artery disease, cerebrovascular disease,

peripheral arterial disease, and hospitalization for heart failure) visited the Hitsumoto Medical Clinic (Yamaguchi, Japan) for the determination of clinical parameters, including the API. A total of 288 hypertensive patients were selected (age: 63 ± 11 years (mean ± standard deviation)).

Ethical considerations

This study was conducted in accordance with the tenets of the Declaration of Helsinki and the ethical standards of the responsible agency for humans. All patients provided informed consent, and the research protocol was performed by the Institutional Review Board Approval of Hitsumoto Medical Clinic (approval number: HMC-2019-7R).

API measurement

API was calculated automatically using a commercially available device (PASESA AVE-1500; Shisei Datum, Tokyo, Japan). Details of API measurements have been previously described [12]. In brief, the blood pressure measurement cuff was wrapped around the upper left arm in a sitting position, pressurized to 190 mm Hg at a rate of 10 mm Hg/s, and depressurized to 10 mm Hg at a rate of 3 mm Hg/s. The cuff pressure during pressurization and depressurization was determined using a pressure transducer. The API is the numerical coefficient of the pressure-volume curve equation obtained by calculating the numerical integration of the mean gradient. Previous studies have shown that the coefficient of variation for repeated measurements on the day of API determination (within an individual of three measurements) is 7.5% [12].

Evaluation of cardiovascular risk factors

The body mass index (body weight (kg)/height squared (m²)) was used as a marker of the degree of obesity. The diagnostic criteria for smoking, diabetes mellitus and dyslipidemia were derived from previous reports [11]. A blood sample was obtained from the peripheral vein in the morning after a 12-h fast; a urine sample was simultaneously collected. The levels of blood glucose, hemoglobin A1c, serum lipid, creatinine, high-sensitivity C-reactive protein, brain natriuretic peptide, and high-sensitivity cardiac troponin T (hs-cTnT) were measured using standard laboratory procedures. The estimated glomerular filtration rate (eGFR), a marker of kidney function, was calculated using a report of a Japanese committee [16]. The levels of brain natriuretic peptide and hs-cTnT were evaluated using commercially available kits (SHIONOSPOT Reader; Shionogi & Co., Osaka, Japan and Roche Diagnostics, Switzerland, respectively) [17]. The levels of urine albumin were evaluated with a commercially available kit (Siemens/Bayer DCA 2000+ Analyzer; Siemens Healthineers, Tokyo, Japan). Skin AF was automatically measured using a commercially available device (AGE Reader™; DiagnOptics, Groningen, Netherlands) [18, 19]. The measurement method was identical to that reported in previous studies. The levels of skin AF were expressed using arbitrary units. A previous study indicated that the level of pentosidine, a major AGE component obtained by skin biopsy, is significantly correlated with skin AF [20]. As an assessment of oral medications, calcium channel blocker (CCB), the renin-angiotensin system (RAS) inhibitor, β-blocker, diuretics, and statins were examined.

Statistical analysis

The StatView J5.0 (HULINKS, Tokyo, Japan) and MedCalc for Windows (version 14.8.1; MedCalc Software, Ostend, Belgium) software were used for statistical analysis. Continuous variables were expressed using the mean and standard deviation. Pearson's or Spearman's rank correlation analysis was used to estimate the correlation coefficient. One-way analysis of variance was utilized to compare the three groups, while *post-hoc* testing was conducted using Fisher's protected least significant differences. Multiple regression analysis was used for multivariate analysis. The Youden's index derived from the ROC curve was calculated [21], to determine the optimal API value for predicting albuminuria, high hs-cTnT, and high skin AF. P-values < 0.05 denoted statistically significant differences.

Results

Patient characteristics

The characteristics of patients included in this study are shown in Table 1. The mean value of the API was 27 ± 5. Figure 1 illustrates the distribution of the API in this study population. The API showed a nearly normal distribution, with a mean value of 27 (range: 16 - 42).

Correlations between the API and biomarkers of CVD

Table 2 shows the correlations between the API and clinical parameters. The API exhibited a relatively strong positive correlation with systolic blood pressure. Regarding its relationships with biomarkers of CVD, the API was significantly positively correlated with the levels of high-sensitivity C-reactive protein, urinary albumin concentrations, brain natriuretic peptide, hs-cTnT, and skin AF. Conversely, the API was significantly negatively correlated with the eGFR.

Comparison of the API in patients treated with CCB and/ or RAS inhibitors

A total of 219 patients received treatment with CCB and/or RAS inhibitors, without other anti-hypertensive drugs. Figure 2 shows the comparison of the API in the three groups (CCB alone (n = 66); RAS inhibitor alone (n = 62); combination of CCB and RAS inhibitors (n = 91)). The API was similar between the CCB alone (API: 27 ± 5) and RAS inhibitor alone

Table 1. Characteristics of Patients

n (male/female)	288 (115/173)
Age (years)	63 ± 11
Body mass index (kg/m^2)	23.0 ± 3.9
Current smoker, n (%)	59 (20)
Systolic blood pressure (mm Hg)	130 ± 18
Diastolic blood pressure (mm Hg)	81 ± 12
Pulse rate (/min)	67 ± 10
Diabetes mellitus, n (%)	132 (46)
Fasting blood glucose (mg/dL)	113 ± 27
Hemoglobin A1c (%)	6.4 ± 0.9
Dyslipidemia, n (%)	189 (66)
Total cholesterol (mg/dL)	216 ± 42
LDL-cholesterol (mg/dL)	139 ± 40
Triglyceride (mg/dL)	146 ± 65
HDL-cholesterol (mg/dL)	49 ± 14
eGFR (mL/min/1.73 m^2)	70 ± 20
Urinary albumin (mg/g Cr)	29 (15 - 51)
hs-CRP (mg/dL)	0.073 (0.034 - 0.166)
BNP (pg/mL)	44.6 (20.0 - 74.3)
hs-cTnT (ng/ml)	0.010 (0.007 - 0.014)
Skin autofluorescence (AU)	2.6 ± 0.5
API	27 ± 5
Medication	
CCB, n (%)	205 (71)
RAS inhibitor, n (%)	157 (55)
β-blocker, n (%)	58 (20)
Diuretics, n (%)	45 (16)
Statin, n (%)	128 (44)

Continuous values are mean ± SD or median (25-75th percentile). LDL: low-density lipoprotein; HDL: high-density lipoprotein; eGFR: estimated glomerular filtration rate; hs-CRP: high-sensitivity C-reactive protein; BNP: brain natriuretic peptide; hs-cTnT: high-sensitivity cardiac troponin T; AU: arbitrary unit; API: arterial pressure-volume index; CCB: calcium channel blocker; RAS: renin-angiotensin system.

(API: 28 ± 5) groups. However, patients receiving treatment with a combination of CCB and RAS inhibitors (API: 25 ± 4) had a significantly lower API than those treated with CCB or RAS inhibitors alone. The levels of systolic blood pressure were significantly lower in patients treated with a combination of CCB and RAS inhibitors than in those receiving treatment with CCB alone or RAS inhibitors alone.

Multivariate analysis

Multiple regression analysis with API as a subordinate factor was performed (Table 3). Examination of the multicollinearity of variables or a stepwise method was conducted for the
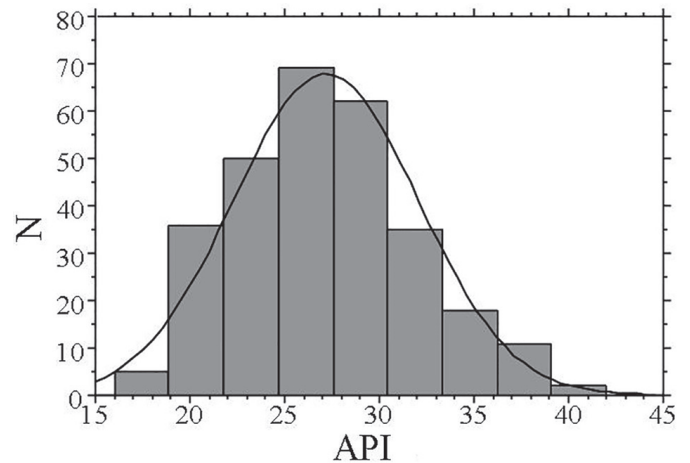

Figure 1. Distribution of API. The API shows a nearly normal distribution, with a mean value of 27 (range: 16 - 42). API: arterial pressure-volume index.

Table 2. Relationship Between API and Various Clinical Parameters

	r	P value
Sex (female = 0, male = 1)	-0.26	< 0.001
Age	0.21	< 0.001
Body mass index	0.10	0.09
Current smoker (no = 0, yes = 1)	0.06	0.28
Systolic blood pressure	0.60	< 0.001
Diastolic blood pressure	0.05	0.45
Pulse rate	-0.10	0.09
Diabetes mellitus (no = 0, yes = 1)	0.11	0.08
Fasting blood glucose	0.03	0.56
Hemoglobin A1c	0.06	0.36
Dyslipidemia (no = 0, yes = 1)	0.05	0.43
Total cholesterol	0.02	0.73
LDL-cholesterol	0.02	0.71
Triglyceride	-0.05	0.43
HDL-cholesterol	-0.07	0.22
eGFR	-0.13	0.03
Log-urinary albumin	0.42	< 0.001
Log-hs-CRP	0.15	0.01
Log-BNP	0.23	< 0.001
Log-hs-cTnT	0.39	< 0.001
Skin autofluorescence	0.41	< 0.001
CCB (no = 0, yes = 1)	-0.16	0.01
RAS inhibitor (no = 0, yes = 1)	-0.15	0.01
β-blocker (no = 0, yes = 1)	0.11	0.08
Diuretics (no = 0, yes = 1)	0.09	0.12
Statin (no = 0, yes = 1)	-0.04	0.47

r expressed correlation coefficient. API: arterial pressure-volume index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; eGFR: estimated glomerular filtration rate; hs-CRP: high-sensitivity C-reactive protein; BNP: brain natriuretic peptide; hs-cTnT: high-sensitivity cardiac troponin T; CCB: calcium channel blocker; RAS: renin-angiotensin system.
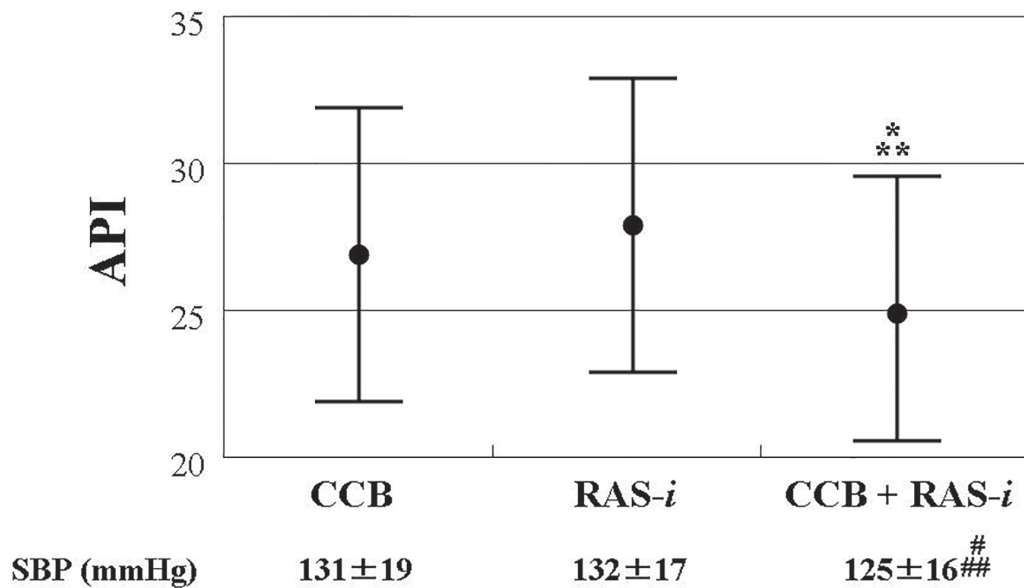
Figure 2. Comparisons of API in patients with CCB and/or RAS inhibitor, showing the comparison of the API in the three groups (CCB alone (n = 66); RAS inhibitor alone (n = 62); combination of CCB and RAS inhibitors (n = 91)). The API was similar between the CCB alone (API: 27 ± 5) and RAS inhibitor alone (API: 28 ± 5) groups. However, patients receiving treatment with a combination of CCB and RAS inhibitors (API: 25 ± 4) had a significantly lower API than those treated with CCB or RAS inhibitors alone. The bars show standard deviation. *P = 0.003 vs. CCB. **P < 0.001 vs. RAS-i. #P = 0.047 vs. CCB, ##P = 0.009 vs. RAS-i. API: arterial pressure-volume index; CCB: calcium channel blocker; RAS-i: renin angiotensin system inhibitor; SBP: systolic blood pressure.

selection of explanatory factors. When the API was used as a subordinate factor, systolic blood pressure, urinary albumin concentration, combination of CCB and RAS inhibitors, hs-cTnT, and skin AF were identified as independent variables.

ROC curve analysis

A ROC curve was generated to detect albuminuria (≥ 30 mg/g Cr), high hs-cTnT concentration (≥ 0.014 ng/mL), or high skin AF (≥ 3.0 arbitrary unit) (Fig. 3) as previously described for

Table 3. Multiple Regression Analysis

Explanatory factor	β	P value
Systolic blood pressure	0.28	< 0.001
Log-urinary albumin	0.15	< 0.001
CCB + RAS inhibitor	-0.14	< 0.001
Log-hs-cTnT	0.13	0.001
Skin autofluorescence	0.11	0.01
Sex (male)	-0.09	0.06
Age	0.07	0.08

Subordinate factor is API. R^2 = 0.52, P < 0.001. Explanatory factors were selected by examining the multicollinearity among the variables or by conducting a stepwise method. CCB: calcium channel blocker; RAS: renin-angiotensin system; hs-cTnT: high-sensitivity cardiac troponin T; β: standardized regression coefficient; API: arterial pressure-volume index; R^2: coefficient of determination.

CVD events [22-24]. The maximum Youden's index revealed that an API > 26 was the optimal cut-off point for determining albuminuria, high hs-cTnT concentration, or high skin AF (area under the curve = 0.703, 0.702, and 0.704; and P < 0.001, respectively).

Discussion

This study demonstrated that API had a high link with systolic blood pressure, and an independent association was observed between the two markers. In current publications, API has a substantial association with systolic blood pressure, similar to this research's results [15]. Nevertheless, API was found to be substantially linked with critical CVD biomarkers, such as urinary albumin concentration, hs-cTnT, and skin AF. Additionally, in multivariate analysis, these biomarkers were chosen as independent drivers of the dependent API, even when corrected for systolic blood pressure. ROC curve analysis indicated that an API > 26 is the ideal cut-off point for estimating albuminuria, high hs-cTnT concentration, or high skin AF, which is often linked with CVD cases. However, this investigation implies that a combination of CCB and RAS inhibitors may effectively reduce API levels.

The API exhibited a significant correlation with biomarkers of kidney function, such as the eGFR and urinary albumin concentrations. Thus, these results indicated that the API was related to kidney function in hypertensive patients. In addition, the levels of urinary albumin were selected as an independ-
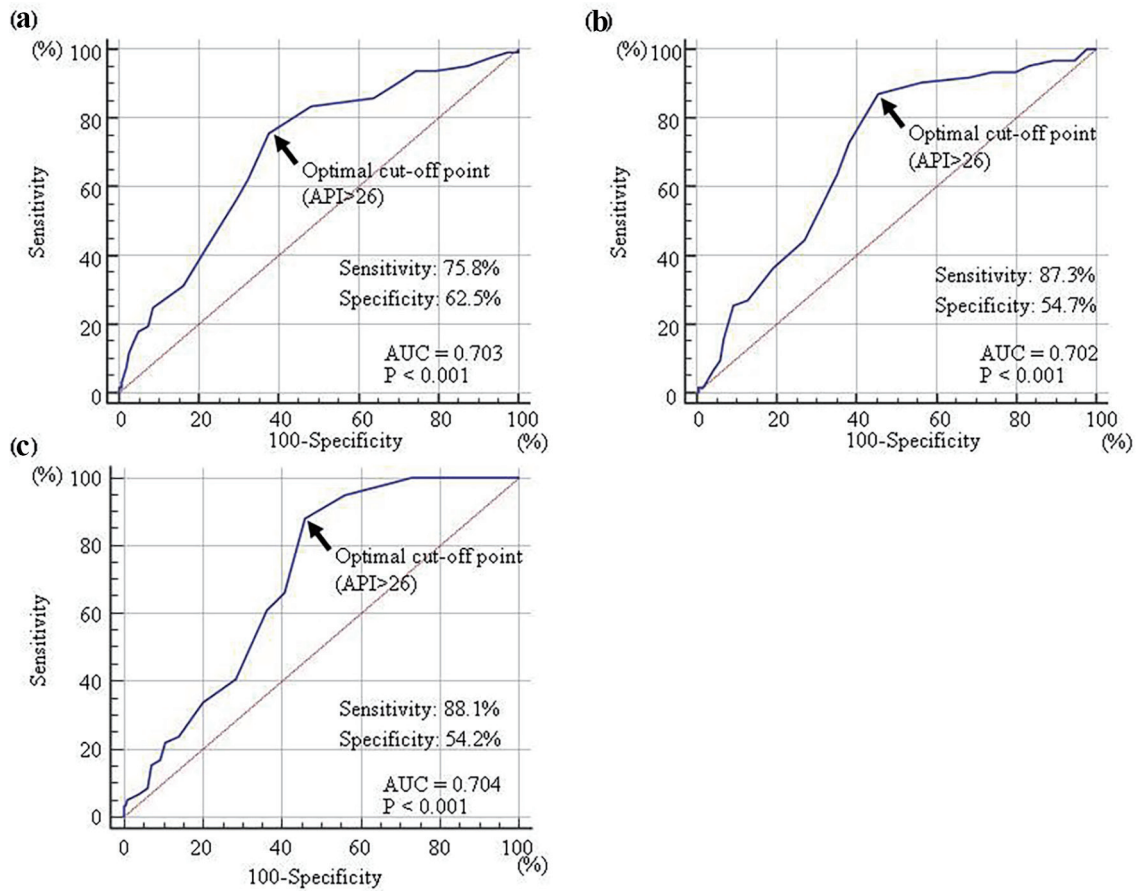
Figure 3. Receiver-operating characteristic curve analysis. The detection of albuminuria (≥ 30 mg/g Cr) (a), high hs-cTnT concentration (≥ 0.014 ng/mL) (b), or high skin AF (≥ 3.0 arbitrary unit) (c) were determined by previous reports. The maximum Youden's index indicated that an API of >26 was the optimal cut-off point for the determination of albuminuria (AUC = 0.703, P < 0.001), high hs-cTnT concentration (AUC = 0.702, P < 0.001), or high skin AF (AUC = 0.704, P < 0.001). API: arterial pressure-volume index; hs-cTnT: high-sensitivity cardiac troponin T; AF: autofluorescence; AUC area under the curve.

ent variable for the API. Researchers reported that these levels are a marker of systemic vascular endothelial function [25]. Therefore, based on these findings, the API may be a physiological marker reflecting vascular endothelial function. However, flow-mediated vasodilation in the brachial artery is also commonly used for assessing vascular endothelial function [26, 27]. Nevertheless, this approach requires certain technical expertise. Therefore, although the API is explored as a parameter of arterial stiffness, it provides the possibility to simply evaluate vascular endothelial function through conventional blood pressure measurement in the sitting position.

Blood troponin levels reflect the degree of myocardial injury. However, several researchers have shown that arterial wall stiffness is significantly associated with biomarkers of myocardial damage [28-30]. A number of investigations have revealed a significant association between left ventricular dysfunction and myocardial injury [31, 32]. In addition, researchers emphasized the increase of aortic artery wall stiffness in the progression of left ventricular dysfunction [33, 34]. Hence, the independent association between hs-cTnT and the API observed in this analysis can be partly attributed to the myocardial damage via left ventricular dysfunction, as a consequence of the worsened artery wall stiffness. Nonetheless, several studies reported a significant association between myocardial injury and coronary atherosclerosis [35, 36]. Ueda et al reported that the API was a significant independent variable linked to the presence of significant coronary stenosis [13]. Of note, patients with a history of coronary artery disease were not included and the coronary artery was not evaluated in this study. Nevertheless, the independent association between hs-cTnT and the API detected in the present investigation may be partly attributed to myocardial injury, which is caused by potential coronary atherosclerosis.

According to numerous studies, AGEs or their receptors are closely linked to the progression of atherosclerosis [37-39]. Moreover, the independent association between skin AF and the API implies that AGEs play an important role in the arterial function of hypertensive patients. However, basic research has shown that anti-hypertensive drugs, such as RAS inhibitors and CCB, decreased the levels of AGEs or their receptors in arterial tissues [40, 41]. Therefore, it is possible that aggressive treatment of patients with hypertension and high skin AF

levels with these medications decreased the incidence of CVD events by reducing the levels of AGEs in arterial wall tissues. However, Isami et al showed that individual lifestyle habits (e.g., sleep, smoking, and dietary content) were independently linked to skin AF levels [42]. Thus, the continuation of appropriate lifestyle habits is also important for maintaining a lower API in hypertensive patients.

Using ROC curve analysis, this investigation established the optimum values of the API to evaluate albuminuria, high hs-cTnT concentration, or high skin AF, which is connected with CVD events. The data indicated that an API > 26 is the optimal cut-off value for determining high levels of these CVD biomarkers. Thus, maintaining an API ≤ 26 in daily clinical practice might decrease the incidence of CVD events in patients with hypertension. In this study, systolic blood pressure levels and combination of RAS inhibitors and CCB were independently associated with the API. CCB or RAS inhibitors are often used in the clinical setting owing to their effectiveness in reducing blood pressure [43]. Furthermore, several studies have shown the benefits of the combination of CCB and RAS inhibitors for the prevention of CVD events in hypertensive patients [44, 45]. Although this was a cross-sectional study, the results emphasize the need to actively attempt to lower the levels of systolic blood pressure using a combination of CCB and RAS inhibitors in hypertensive patients with a high API. This approach may consequently prevent the occurrence of CVD events in the future.

Limitations

The drawbacks of this research are outlined below. First, the independent relationship between the API and systolic blood pressure was discovered. Considering that API is hinged on systolic blood pressure at the estimation time increased API than proper stiffness might be derived in hypertensive patients. Further investigations are required to better understand the characteristics of API as a biomarker of arterial stiffness. Second, based on the findings of ROC curve analysis, an API > 26 was calculated as an estimated value for the risk of experiencing CVD. However, this investigation is cross-sectional, and it is essential to assess the reliability of API > 26 through further investigation in the future.

Conclusions

This study demonstrates that API had an independent relationship with crucial CVD indicators, such as urinary albumin, high-sensitivity troponin T, and skin AF. Additionally, the ROC curve analysis results are displayed as values with API > 26 defined for these indicators linked with the formation of CVD. Future investigations concentrating on API in hypertensive patients must validate these findings.

Acknowledgments

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in this study.

Conflict of Interest

None to declare.

Informed Consent

Informed consent was obtained from all patients who participated in this study.

Author Contributions

TH contributed to the research planning, data acquisition and analysis, and manuscript writing and editing.

Data Availability

The author declares that data supporting the findings of this study are available within the article.

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