Experimental and Clinical Cardiology

Association between major adverse cardiovascular events and brachial-ankle pulse wave velocity and a difference in blood pressure between arms after percutaneous coronary intervention

Original article

Yoshihisa Nagata[1], Shin-ichiro Miura[1,2], Yasunori Suematsu[1], Makoto Sugihara[1], Amane Ike[1], Atsushi Iwata[1], Hiroaki Nishikawa[1], Akira Kawamura[1], Keijiro Saku[1,2].

1 Department of Cardiology, Fukuoka University School of Medicine, Fukuoka, 814-0180, Japan.
2 Department of Molecular Cardiovascular Therapeutics, Fukuoka University School of Medicine, Fukuoka, 814-0180, Japan.

Running Title: MACE and baPWV or bilateral blood pressure
Address correspondence to: Shin-ichiro Miura, Department of Cardiology, Fukuoka University School of Medicine, 7-45-1 Nanakuma, Jonan-ku, Fukuoka, 814-0180, Japan. Tel: 81-92-801-1011; Fax: 81-91-865-2692; E-mail:miuras@cis.fukuoka-u.ac.jp

Abstract Arterial stiffness is well known to be an important risk factor for cardiovascular events. Although brachial-ankle pulse wave velocity (baPWV) and bilateral blood pressure (BP) in the arms are measured routinely, it is uncertain whether baPWV and the difference in BP between the arms could predict major adverse cardiovascular events (MACE) after elective percutaneous coronary intervention (PCI). We retrospectively examined 398 stable angina patients who underwent successful bare metal stent (BMS) or drug-eluting stent (DES) implantation and in whom we could measure lt. and rt. baPWV and BP in both arms. We also calculated the absolute (|rt. BP-lt. BP|) and relative (rt. BP-lt. BP) differences in systolic BP (SBP) and diastolic BP between the arms. During the follow-up period (9±3 months), 13 % of the total patients had MACE [all-cause death, myocardial infarction, target lesion revascularization (PCI or coronary artery bypass grafting)]. In a multivariate analysis, stent size, left ventricular ejection fraction, type of stent and insulin use were significantly associated with MACE in all patients. In the BMS group, stent size was significantly associated with MACE. Interestingly, in patients with DES implantation, the relative difference in SBP between arms, lt. baPWV and insulin use were independent predictors of MACE. The cut-off levels of lt. baPWV and relative SBP between the arms for predicting MACE were 1854 cm/sec and 0 mmHg, respectively. In conclusion, both the relative difference in SBP between the arms and baPWV in addition to insulin use predicted MACE after DES implantation, but not BMS implantation.

Key words: brachial-ankle pulse wave velocity, bilateral blood pressure, major adverse cardiovascular events, percutaneous coronary intervention, stable angina patients.

1. Introduction

Arterial stiffness is an important predictive factor for cardiovascular (CV) events [1, 2] and is associated with arteriosclerosis [3]. Measurements of arterial stiffness are increasingly being used in clinical studies. Brachial ankle pulse wave velocity (baPWV) is currently a conventional measurement for arterial stiffness in a clinical setting [4]. It is important to determine this parameter with noninvasive automatic devices. The use of pressure cuffs wrapped on the upper arm and ankle is very simple, reproducible and inexpensive [5]. Thus, this is an easier method for screening the general population than other methods for measuring arterial stiffness. Many studies have demonstrated that baPWV predicts cardiovascular events in a general population or in patients with either hypertension (HTN), diabetes mellitus (DM), end-stage renal failure (ESRD) or acute coronary syndrome (ACS) [6-10].

Moreover, the method used to measure baPWV reflects the stiffness of both the aorta and peripheral artery in an arm and a leg and can be used to obtain bilateral brachial blood pressure (BP) measurements. Although the need to check BP in both arms has been recognized, most general practitioners do not follow this advice. Recently, Clark *et al.* showed that a difference in systolic BP (SBP) of more than 10 mmHg between arms was associated with vascular disease and mortality [11]. In addition, a difference in SBP between arms could be a novel risk marker for diabetic nephropathy in patients with Type 2 diabetes [12]. Thus, we should measure BP in both arms.

However, very little information is available on the association between CV events and either baPWV or a difference in BP between the arms in patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI). To the best our knowledge, there is no clear and significant marker of revascularization in current clinical practice. Consequently, we hypothesized that baPWV and/or a difference in BP between the arms could be a better predictor of CV events than conventional coronary risk factors in patients with CAD after PCI. Since the rate of in-stent restenosis after bare metal stent (BMS) implantation was shown to be much higher than that after drug-eluting stent (DES) implantation [13-15], we evaluated the associations between these parameters and MACE in all patients and in patients with BMS or DES implantation.

2. Methods

2.1 Study population

From March 2003 to December 2012, we retrospectively enrolled 539 patients who underwent successful PCI and in whom we could measure baPWV and BP in both arms at Fukuoka University Hospital. The patients had at least 1 significant stenotic lesion with >50% diameter stenosis (DS). Patients who underwent plain old balloon angioplasty (POBA), who were diagnosed as ACS or who had ESRD or were on hemodialysis were excluded. Finally, we selected 398 stable angina patients (297 males, 101 females; 68±11 years) who underwent successful BMS or DES implantation. All patients were diagnosed with stable angina by a history of chest pain, coronary angiography (CAG), electrocardiogram and multi-detector-row computed tomography. Our protocol was approved by the ethics committee of Fukuoka University Hospital. We retrospectively collected and analyzed all data using the database of Fukuoka University Hospital.

2.2 Cardiovascular risk factors and biochemical parameters in blood

We collected information regarding the patient's coronary risk factors including HTN, DM, dyslipidemia (DL) and current smoking in addition to prior myocardial infarction (MI), prior PCI, prior CABG and current medications. Height and weight were measured for all patients, and body mass index [BMI, weight (kg)/height $(m)^2$] was calculated. Data on biochemical parameters in blood including low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), estimated glomerular filtration rate (eGFR) and glycated hemoglobin A1c (HbA1c) were also collected.

2.3 Measurements of baPWV, bilateral BP, ankle-brachial Index (ABI) and left ventricular ejection fraction (LVEF)

Bilateral baPWV, bilateral BP and ABI were measured during hospitalization or within one month before and after PCI. After the patient had rested in a supine position for at least 5 minutes, baPWV was measured using a volume plethysmographic device (Omron Healthcare, Kyoto, Japan), which uses a method based on BP cuffs wrapped on the arm near the brachial artery and near the tibial artery of the ankle [16]. We recorded BP in both arms, ABI and bilateral baPWV. Mean baPWV was calculated as (lt. baPWV + rt. baPWV)/2. We also calculated the absolute (|rt. BP - lt. BP|) and relative (rt. BP - lt. BP) differences in SBP and diastolic BP (DBP) between the arms. LVEF was measured by ultrasound cardiography before PCI.

2.4 CAG

CAG and PCI were performed according to the Judkins technique by the patients' interventional cardiologists [17]. Coronary angiograms were analyzed with respect to the 15-segment coding system of the American Heart Association [18], and significant stenosis or restenosis was considered to be >50% DS. PCI was performed either ad-hoc or after loading antiplatelets. Patients received either BMS or DES based on the judgment of their cardiologists.

2.5 Major adverse cardiovascular events (MACE)

During the follow-up period (9±3 months), MACE [all-cause death, myocardial infarction (MI), target lesion revascularization (TLR-PCI and TLR-coronary artery bypass grafting (CABG)] were analyzed. The definition of MI included ST-T and non ST-T elevation. For a diagnosis of MI, the patient had to have satisfied the following criteria: evidence of ischemic

electrocardiogram changes and elevation of cardiac enzymes. Stent thrombosis was defined according to the Academic Research Consortium criteria [19]. TLR was performed if the lesion had significant luminal stenosis (>50% DS) in the presence of angina symptoms and/or proven myocardial ischemia in the target vessel, or in follow-up CAG. All-cause death was identified throughout the follow-up period.

2.6 Statistical analysis

Statistical analysis was performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA) at Fukuoka University. A one-way analysis of variance and a contingency table analysis were used for intergroup comparisons of categorical variables. For intergroup comparisons of continuous variables, we used Student's t-test and a contingency table analysis. We also used a multiple logistic regression analysis for the multivariate analysis to evaluate independent predictors of MACE. A receiver-operating characteristic (ROC) curve analysis was used to determine the cut-off of the lt. baPWV and the relative SBP between arms to distinguish between with and without MACE at the highest possible sensitivity and specificity levels. Values are expressed as mean ± standard deviation (SD). Statistical significance was defined as a p-value less than 0.05.

3. Results

3.1 Patient characteristics at baseline in all patients

The patient characteristics at baseline in all patients are shown in Table 1. Fifty-two of the overall patients (13 %) had MACE. The mean age of all patients and patients with and without MACE was 68±10, 69±9 and 67±11 years, respectively. Patients with MACE showed significantly lower percentages of DL and DES implantation, lower levels of LVEF and TG and smaller stent size than patients without MACE. In addition, patients with MACE showed a significantly higher percentage of insulin use. There were no significant differences in conventional coronary risk factors (BMI and percentages of DL, HTN, DM and smoking) except for DL between patients with and without MACE.

3.2 Patient characteristics at baseline in patients with BMS and DES implantation

Next, all patients were divided into two groups (BMS and DES implantation), since the rate of in-stent restenosis after BMS implantation was shown to be much higher than that after DES implantation [13-15] and since the type of stent and stent size may affect the presence of MACE. Patient characteristics at baseline in patients with BMS and DES implantation are shown in Tables 2 and 3, respectively. The percentage of MACE in patients with DES implantation (10 %) was significantly lower than that in patients with BMS implantation (18 %). In patients with BMS implantation, patients with MACE showed significantly lower levels of LVEF, rt. DBP, TG, and HDL-C and smaller stent size than patients without MACE (Table 2). In addition, patients with MACE showed a significantly higher percentage of β-blocker use. On the other hand, among patients with DES implantation, patients with MACE showed significantly higher levels of lt. baPWV and mean PWV and higher percentages of right coronary artery (RCA) as the target lesion and insulin use (Table 3). Patients with MACE showed a significantly lower level of relative SBP between the arms.

3.3 Predictors of MACE in all patients and in patients with BMS and DES implantation

Predictors of MACE as assessed by a multiple logistic regression analysis in all patients and in patients with BMS and DES implantation are shown in Figs. 1, 2 and 3, respectively. In all patients, we selected factors that were significantly different (percentage of DL, LVEF, type of stent, stent size, insulin use and TG) between those with and without MACE, as shown in Table 1, in addition to age, gender, BMI and conventional coronary risk factors (HTN, DL, DM and smoking) as independent variables. MACE in all patients was independently associated with LVEF (p=0.005), stent size (p=0.018), type of stent (p=0.016) and insulin use (p=0.002) (Fig. 1). Next, we analyzed predictors of MACE in patients with BMS implantation. We selected factors that were significantly different (LVEF, rt. DBP, stent size, β-blocker, TG and HDL-C) between patients with and without MACE as shown in Table 2, in addition to age, gender, BMI and conventional coronary risk factors as independent variables. MACE in patients with BMS implantation was independently associated with stent size (p=0.008) (Fig. 2). Finally, we also analyzed predictors of MACE in patients with DES implantation. We selected factors that were significantly different (lt. baPWV, relative SBP between arms, percentages of RCA as the target lesion and insulin use) between patients with and without MACE as shown in Table 3, in addition to age, gender, BMI and conventional coronary risk factors as independent variables. We excluded mean baPWV and selected lt. baPWV as an independent variable because mean

Table 1. Patients characteristics, baPWV, BP, ABI, target lesion characteristics, medications, biochemical parameters in blood and MACE in patients without and with MACE in all patients.

	All (n=398)	MACE (-) (n=346)	MACE (+) (n=52)	P value MACE (-) vs. MACE (+)
Age, years	68±10	67±11	69±9	0.167
Male, n (%)	297 (75)	258 (75)	39 (75)	1.000
BMI, kg/m^2	24.0±13.3	24.0±3.3	23.5±3.1	0.291
HTN, n (%)	321 (81)	282 (82)	39 (75)	0.263
DL, n (%)	324 (81)	288 (83)	36 (69)	0.021
DM, n (%)	182 (46)	157 (45)	25 (48)	0.766
Smoking, n (%)	164 (41)	144 (42)	20 (39)	0.763
Prior MI, n (%)	93 (23)	83 (24)	10 (19)	0.598
Prior PCI, n (%)	102 (26)	92 (27)	10 (19)	0.309
Prior CABG, n (%)	12 (3)	10 (3)	2 (3.9)	0.662
UCG-LVEF, %	63±13	63±12	58±15	0.003
baPWV, BP and ABI				
rt. baPWV, cm/sec	1801±404	1805±409	1842±375	0.534
lt. baPWV, cm/sec	1811±405	1803±407	1866±394	0.294
Mean baPWV, cm/sec	1806±406	1799±410	1854±381	0.358
rt. SBP, mmHg	131±20	132±20	130±23	0.603
lt. SBP, mmHg	131±21	131±21	131±23	0.896
Mean SBP, mmHg	131±20	131±20	130±23	0.744
Relative SBP, mmHg	0.54±9.54	0.69±5.97	-0.48±5.67	0.186
Absolute SBP, mmHg	3.92±4.49	3.92±4.56	3.94±4.06	0.972
rt. DBP, mmHg	76±11	76±11	73±12	0.081
lt. DBP, mmHg	76±11	76±11	74±11	0.250
Mean DBP, mmHg	76±11	76±11	74±11	0.139
Relative DBP, mmHg	-0.37±4.57	-0.24±4.34	-1.27±5.86	0.228
Absolute DBP, mmHg	2.91±3.54	2.79±3.33	3.69±4.70	0.189
rt. ABI	1.1±0.1	1.1±0.1	1.1±0.1	0.386
lt. ABI	1.1±0.1	1.1±0.1	1.1±0.1	0.962
Mean ABI	1.1±0.1	1.1±0.1	1.1±0.1	0.327
Target lesion characteristics				
RCA, n (%)	104 (26)	87 (25)	17 (33)	0.242
LMT, n (%)	8 (2)	7 (2)	1 (2)	1.000
LAD, n (%)	213 (54)	187 (54)	26 (50)	0.654
LCX, n (%)	73 (18)	65 (19)	8 (15)	0.701
DES/BMS, n (%)	259/139 (65/35)	232/114 (67/33)	27/25 (52/48)	0.042
Stent size, mm	3.1±0.4	3.1±0.4	2.9±0.4	0.019
Stent length mm	21.1±6.0	21.1±6.0	21.4±5.9	0.699
Medications				
ACE-I or ARB, n (%)	292 (73)	256 (74)	36 (69)	0.502
CCB, n (%)	205 (52)	180 (52)	25 (48)	0.656
β-blocker, n (%)	60 (15)	48 (14)	12 (23)	0.096
Diuretics, n (%)	69 (17)	59 (17)	10 (19)	0.696
Statins, n (%)	306 (77)	266 (77)	40 (77)	1.000
Nitrate, n (%)	94 (24)	85 (25)	9 (17)	0.296
Nicorandil, n (%)	108 (27)	94 (27)	14 (27)	1.000
SU, n (%)	52 (13)	45 (13)	7 (14)	1.000
α-GI, n (%)	51 (13)	42 (12)	9 (17)	0.275
DPP-4I, n (%)	10 (3)	10 (3)	0 (0)	0.372
Insulin, n (%)	48 (12)	35 (10)	13 (25)	0.005
Biochemical parameters in blood				
eGFR	64.0±19.3	64.4±19.1	61.1±20.2	0.253
TG, mg/dL	140±83	144±86	118±57	0.005
HDL-C, mg/dL	48±16	49±16	48±12	0.643
LDL-C, mg/dL	108±33	108±33	107±30	0.742
HbA1c, %	6.4±1.4	6.3±1.4	6.6±1.7	0.330
MACE				
MI, n (%)	11 (3)	0 (0)	11 (21)	N.D.
TLR-PCI, n (%)	37 (9)	0 (0)	37 (71)	N.D.
TLR-CABG, n (%)	8 (2)	0 (0)	8 (15)	N.D.
Death, n (%)	4 (1)	0 (0)	4 (8)	N.D.
ISR, n (%)	64 (16)	17 (5)	47 (90)	<0.0001

Continuous variables are expressed as mean ± SD. BMI, body mass index; HTN, hypertension; DL dyslipidemia; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; UCG-LVEF, ultrasound cardiography-left ventricular ejection fraction; baPWV, brachial-ankle pulse wave velocity; BP, blood pressure; rt., right; lt., left; SBP, systolic BP; DBP, diastolic BP; ABI, ankle-brachial index; RCA, right coronary artery; LMT, left main trunk; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; DES, drug-eluting stent; BMS, bare-metal stent; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; SU, sulfonylurea; α-GI, α-glucosidase inhibitor; DPP-4I, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycated hemoglobin A1c; TLR, target lesion revascularization; ISR, in-stent restenosis. N.D., not determined.

Table 2. Patients characteristics, baPWV, BP, ABI, target lesion characteristics, medications, biochemical parameters in blood and MACE in patients without and with MACE in BMS implantation.

	BMS (n=139)	MACE (-) (n=114)	MACE (+) (n=25)	P value MACE (-) vs. MACE (+)
Age, years	67±12	66±12	70±9	0.139
Male, n (%)	106 (76)	86 (75)	20 (80)	0.797
BMI, kg/m^2	24.4±3.6	24.4±3.7	24.1±3.1	0.667
HTN, n (%)	103 (74)	87 (76)	16 (64)	0.215
DL, n (%)	110 (79)	93 (82)	17 (68)	0.172
DM, n (%)	56 (40)	48 (42)	8 (32)	0.379
Smoking, n (%)	58 (42)	47 (41)	11 (44)	0.826
Prior MI, n (%)	31 (22)	26 (23)	5 (20)	1.000
Prior PCI, n (%)	27 (19)	24 (21)	3 (12)	0.408
Prior CABG, n (%)	6 (4)	5 (4)	1 (4)	1.000
UCG-LVEF, %	62±13	64±12	54±16	0.001
baPWV, BP and ABI				
rt. baPWV, cm/sec	1819±430	1836±450	1742±317	0.222
lt. baPWV, cm/sec	1829±435	1844±453	1759±336	0.376
Mean baPWV, cm/sec	1824±429	1840±449	1750±323	0.346
rt. SBP, mmHg	130±20	131±19	126±22	0.217
lt. SBP, mmHg	130±20	131±20	125±23	0.166
Mean SBP, mmHg	130±20	131±19	125±22	0.186
Relative SBP, mmHg	0.25±5.20	0.10±5.24	0.96±5.04	0.454
Absolute SBP, mmHg	3.85±3.49	3.78±3.61	4.16±2.88	0.624
rt. DBP, mmHg	76±12	77±11	71±12	0.032
lt. DBP, mmHg	76±12	77±12	73±11	0.153
Mean DBP, mmHg	76±11	77±11	72±11	0.068
Relative DBP, mmHg	-0.71±4.64	-0.38±3.81	-2.20±7.24	0.232
Absolute DBP, mmHg	2.96±3.62	2.64±2.76	4.44±6.08	0.159
rt. ABI	1.1±0.1	1.1±0.1	1.1±0.1	0.552
lt. ABI	1.1±0.1	1.1±0.1	1.1±0.1	0.902
Mean ABI	1.1±0.1	1.1±0.1	1.1±0.2	0.824
Target lesion characteristics				
RCA, n (%)	47 (34)	41 (36)	6 (24)	0.351
LMT, n (%)	2 (1)	1 (1)	1 (4)	0.328
LAD, n (%)	69 (50)	57 (50)	12 (48)	1.000
LCX, n (%)	21 (15)	15 (13)	6 (24)	0.215
Stent size, mm	3.2±0.5	3.3±0.5	3.0±0.4	0.001
Stent length mm	19.0±5.6	18.8±5.3	19.9±6.5	0.400
Medications				
ACE-I or ARB, n (%)	99 (71)	81 (71)	18 (72)	1.000
CCB, n (%)	65 (47)	54 (47)	11 (44)	0.827
β-blocker, n (%)	22 (16)	14 (12)	8 (32)	0.029
Diuretics, n (%)	24 (17)	19 (17)	5 (20)	0.770
Statins, n (%)	98 (71)	80 (70)	18 (72)	1.000
Nitrate, n (%)	33 (24)	28 (25)	5 (20)	0.797
Nicorandil, n (%)	42 (30)	36 (32)	6 (24)	0.631
SU, n (%)	14 (10)	11 (10)	3 (12)	0.717
α-GI, n (%)	14 (10)	11 (10)	3 (12)	0.717
DPP-4I, n (%)	3 (2)	3 (3)	0 (0)	1.000
Insulin, n (%)	13 (9)	9 (8)	4 (16)	0.251
Biochemical parameters in blood				
eGFR	65.9±19.8	66.1±20.4	62.6±16.8	0.431
TG, mg/dL	147±98	153±104	116±52	0.010
HDL-C, mg/dL	48±17	49±19	43±10	0.034
LDL-C, mg/dL	118±34	119±34	113±32	0.458
HbA1c, %	6.3±1.5	6.3±1.5	6.2±1.3	0.772
MACE				
MI, n (%)	4 (3)	0 (0)	4 (16)	N.D.
TLR-PCI, n (%)	18 (13)	0 (0)	18 (72)	N.D.
TLR-CABG, n (%)	4 (3)	0 (0)	4 (16)	N.D.
Death, n (%)	1 (1)	0 (0)	1 (4)	N.D.
ISR, n (%)	32 (12)	9 (4)	23 (85)	<0.0001

Abbrevaitions as shown in Table 1.

Table 3. Patients characteristics, baPWV, BP, ABI, target lesion characteristics, medications, biochemical parameters in blood and MACE in patients without and with MACE in DES implantation.

	DES (n=259)	MACE (-) (n=232)	MACE (+) (n=27)	P value MACE (-) vs. MACE (+)
Age, years	68±10	68±10	69±9	0.618
Male, n (%)	191 (74)	172 (74)	19 (70)	0.650
BMI, kg/m^2	23.7±3.1	23.8±3.1	23.0±3.1	0.175
HTN, n (%)	218 (84)	195 (84)	23 (85)	1.000
DL, n (%)	214 (83)	195 (84)	19 (70)	0.103
DM, n (%)	126 (49)	109 (47)	17 (63)	0.154
Smoking, n (%)	106 (41)	97 (42)	9 (33)	0.536
Prior MI, n (%)	62 (24)	57 (25)	5 (19)	0.636
Prior PCI, n (%)	75 (29)	68 (29)	7 (26)	0.825
Prior CABG, n (%)	6 (2)	5 (2)	1 (4)	0.487
UCG-LVEF, %	63±13	63±13	61±13	0.363
baPWV, BP and ABI				
rt. baPWV, cm/sec	1805±390	1790±386	1936±406	0.066
lt. baPWV, cm/sec	1802±389	1783±381	1966±424	0.020
Mean baPWV, cm/sec	1796±394	1778±389	1951±410	0.031
rt. SBP, mmHg	132±21	132±21	134±23	0.599
lt. SBP, mmHg	132±21	131±21	136±22	0.245
Mean SBP, mmHg	132±21	131±21	135±22	0.391
Relative SBP, mmHg	0.69±6.31	0.98±6.29	-1.81±5.97	0.029
Absolute SBP, mmHg	3.96±4.95	3.99±4.96	3.74±4.96	0.807
rt. DBP, mmHg	76±11	76±11	75±12	0.705
lt. DBP, mmHg	76±11	76±11	75±11	0.778
Mean DBP, mmHg	76±11	76±11	75±11	0.735
Relative DBP, mmHg	-0.20±4.54	-0.17±4.59	-0.41±4.17	0.800
Absolute DBP, mmHg	2.88±3.50	2.87±3.57	3.00±2.87	0.856
rt. ABI	1.1±0.1	1.1±0.1	1.1±1.1	0.460
lt. ABI	1.1±0.1	1.1±0.1	1.1±0.1	0.654
Mean ABI	1.1±0.1	1.1±0.1	1.1±0.1	0.146
Target lesion characteristics				
RCA, n (%)	57 (22)	46 (20)	11 (41)	0.024
LMT, n (%)	6 (2)	6 (3)	0 (0)	1.000
LAD, n (%)	144 (56)	130 (56)	14 (52)	0.541
LCX, n (%)	52 (20)	50 (22)	2 (7)	0.124
Stent size, mm	3.0±0.4	3.0±0.4	2.9±0.4	0.382
Stent length mm	22.3±5.9	22.2±6.0	22.9±4.9	0.547
Medications				
ACE-I or ARB, n (%)	193 (75)	175 (75)	18 (67)	0.352
CCB, n (%)	140 (54)	126 (54)	14 (52)	0.841
β-blocker, n (%)	38 (15)	34 (15)	4 (15)	1.000
Diuretics, n (%)	45 (17)	40 (17)	5 (19)	0.793
Statins, n (%)	208 (80)	186 (80)	22 (82)	1.000
Nitrate, n (%)	61 (24)	57 (25)	4 (15)	0.341
Nicorandil, n (%)	66 (26)	58 (25)	8 (30)	0.642
SU, n (%)	38 (15)	34 (15)	4 (15)	1.000
α-GI, n (%)	37 (14)	31 (13)	6 (22)	0.242
DPP-4I, n (%)	7 (3)	7 (3)	0 (0)	1.000
Insulin, n (%)	35 (14)	26 (11)	9 (33)	0.004
Biochemical parameters in blood				
eGFR	63.2±19.0	63.6±18.4	59.8±23.2	0.320
TG, mg/dL	137±73	139±74	119±95	0.190
HDL-C, mg/dL	49±14	48±15	52±14	0.268
LDL-C, mg/dL	103±31	103±32	101±28	0.684
HbA1c, %	6.4±1.4	6.4±1.3	6.9±1.9	0.150
MACE				
MI, n (%)	7 (3)	0 (0)	7 (26)	N.D.
TLR-PCI, n (%)	19 (7)	0 (0)	19 (70)	N.D.
TLR-CABG, n (%)	4 (2)	0 (0)	4 (15)	N.D.
Death, n (%)	3 (1)	0 (0)	3 (11)	N.D.
ISR, n (%)	32 (23)	8 (7)	24 (96)	<0.0001

Abbrevaitions as shown in Table 1.

baPWV was significantly associated with lt. baPWV and the p value of lt. baPWV (p=0.020) was lower than that of mean PWV (p=0.031) as shown in Table 3. MACE in patients with DES implantation was independently associated with lt. baPWV (p=0.041), relative SBP between the arms (p=0.026) and insulin use (p=0.004) (Fig. 3). Thus, conventional coronary risk factors in addition to age, gender and BMI were not associated with MACE in all patients or in patients with BMS or DES implantation.

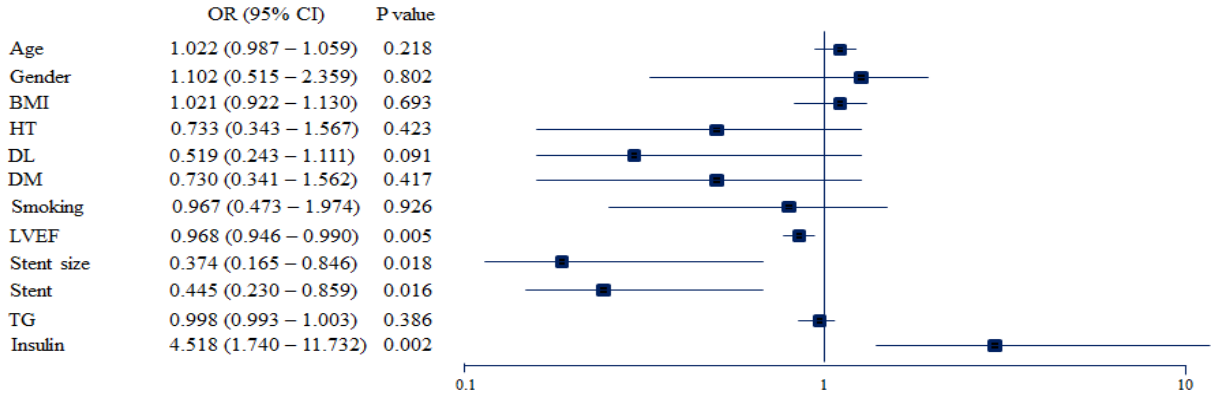

Figure 1. Logistic regression analysis for MACE in all patients using independent variables.

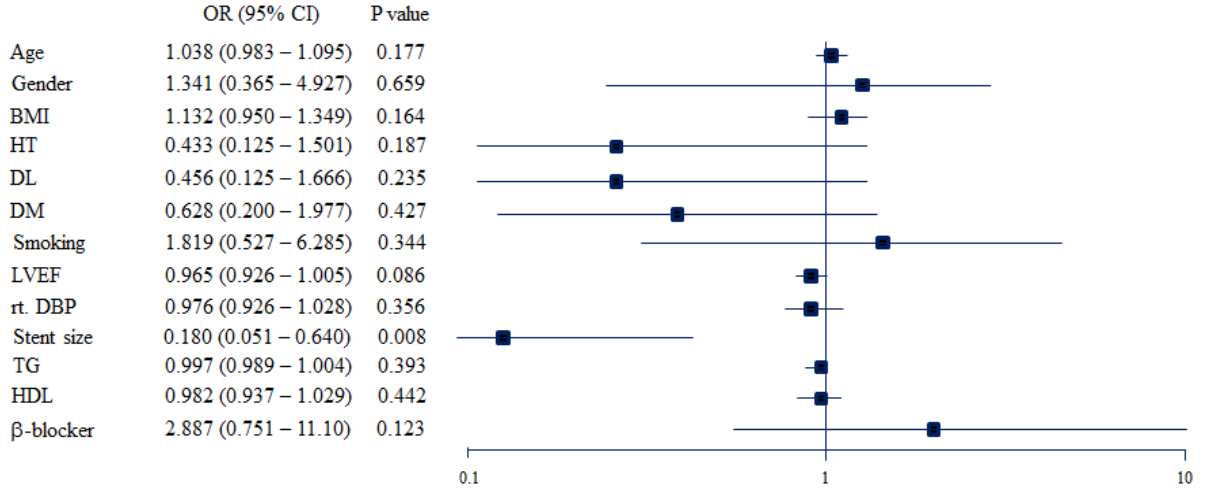

Figure 2. Logistic regression analysis for MACE in patients with BMS implantation using independent variables.

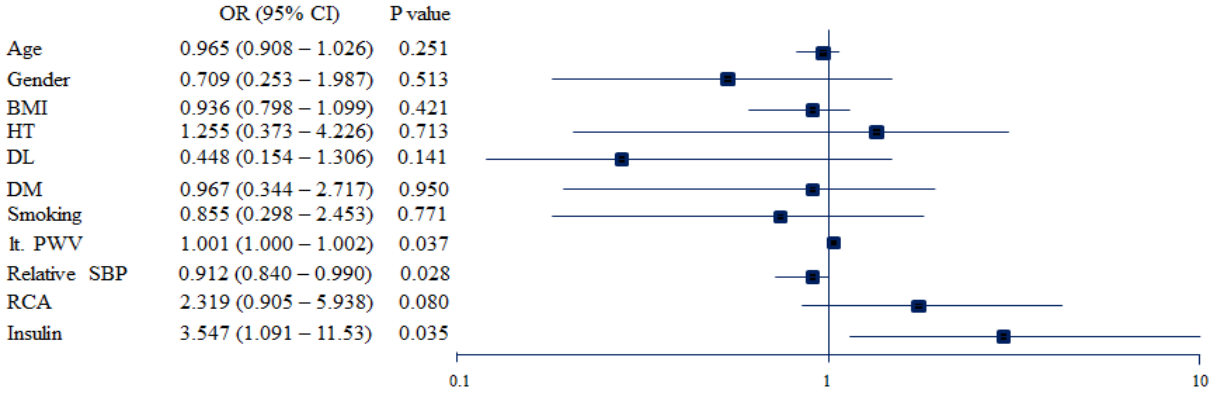

Figure 3. Logistic regression analysis for MACE in patients with DES implantation using independent variables.

3.4 Sensitivity and specificity of the level of lt. baPWV and relative SBP between the arms for predicting MACE in patients with DES implantation

For patients with DES implantation, the sensitivity and specificity of lt. baPWV and relative SBP between the arms for predicting MACE were examined by an ROC analysis. The cut-off level of lt. baPWV that gave the greatest sensitivity and specificity for MACE was 1854 cm/sec [area under the curve (AUC) = 0.613, sensitivity = 0.634 and specificity = 0.593]. As shown in Fig. 4, the cut-off level of relative SBP between the arms that gave the greatest sensitivity and specificity for MACE was 0 mmHg (AUC = 0.623, sensitivity = 0.621 and specificity = 0.556).

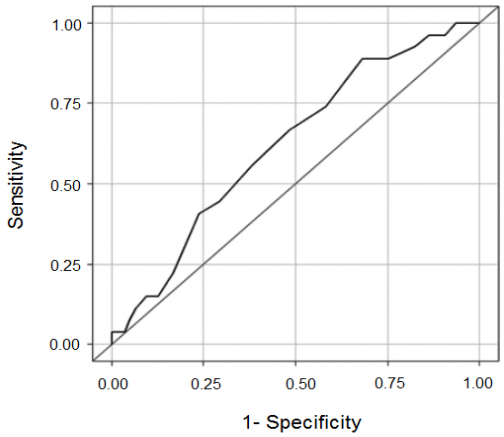

Figure 4. Receiver-operating characteristic (ROC) curve for the relative SBP between arms for MACE in patients with DES implantation.

4. Discussion

In the present study, we hypothesized that baPWV and a relative and/or an absolute difference in BP between arms may be better predictors of CV events than conventional coronary risk factors in patients with CAD after PCI. Unexpectedly, neither baPWV nor a difference in BP between the arms was a predictor of MACE in patients with stable angina after stent implantation in all patients. In addition, conventional coronary risk factors in addition to age, gender and BMI were not associated with MACE in all patients or in patients with BMS or DES implantation. Interestingly, MACE in patients with DES implantation was independently associated with lt. baPWV and a relative SBP between the arms.

Since the type of stent and stent size were predictors of MACE overall (Fig. 1), all of the patients were divided into patients with BMS implantation and DES implantation to analyze the predictors of MACE after stent implantation (Figs. 2 and 3). Interestingly, the predictors of MACE in patients with DES implantation (lt. PWV, a relative difference in SBP between arms and insulin use) were much different from those in patients with BMS implantation (stent size). The percentage of TLR-PCI plus TLR-CABG in MACE in patients with BMS and DES implantation was 88 % and 85 %, respectively. Since most MACE was TLR-PCI plus TLR-CABG due to in-stent restenosis (ISR), and since the rate of restenosis in patients with DES implantation (12 %) was much lower than that in patients with BMS implantation (23 %), this may affect the differences in predictors of MACE after stent implantation between patients with BMS and DES implantation. In addition, there was no difference in TLR in larger vessels for PCI in either BMS or DES [20]. However, a small vessel size for PCI was associated with an increase in TLR in patients implanted with BMS [21]. Implantation of a smaller BMS was more significantly related to target vessel revascularization than DES implantation [22]. In this study, stent size with MACE was significantly smaller than that without MACE in patients with BMS implantation, whereas there was no difference in stent size between patients with and without MACE among those with DES implantation. A smaller stent strongly affected the predictors of MACE in patients with BMS implantation, and other predictors of MACE may be canceled by this strong predictor in this study.

A relative difference in SBP between arms was a predictor of MACE in patients with DES implantation in this study, although a relative BP difference between arms is unrelated to age, gender, ethnicity, arm circumference and handedness [23]. BP in the rt. arm is generally higher than that in the lt. arm in healthy subjects [24-26], perhaps because the rt. subclavian artery is closer to the heart than the lt. subclavian artery [27]. Among patients with MACE and DES implantation, BP in the lt. arm was higher than that in the rt. arm. Interestingly, the cut-off level of relative SBP between arms that gave the greatest sensitivity and specificity for MACE was 0 mmHg in patients with DES implantation. They did not show a general difference in BP between arms probably due to the progression of atherosclerosis in the subclavian artery. Further studies will be needed to clarify this issue.

An absolute BP difference was shown to be a novel risk marker for diabetic nephropathy in patients with DM and was associated with coronary risk factors in a general population in Japan [12, 28, 29]. An absolute difference in SBP of more than 10 mmHg between arms has been associated with vascular disease and mortality [11]. These reports indicated that an absolute difference in BP is more important than a relative difference in BP. In this study, the absolute differences in SBP and DBP were only about 4 mmHg and 3 mmHg in both patients with BMS and DES implantation. Among all of the patients, only 26 had an absolute BP difference of more than 10 mmHg. This may be why the absolute difference in BP was not important for predicting MACE in this study.

baPWV was also a predictor of MACE in patients with DES implantation. Increased baPWV is associated with the development of endothelial dysfunction [30, 31] and atherosclerosis [3], and higher levels of baPWV were associated with the risk and severity of CAD [32]. Munk *et al.* indicated that endothelial dysfunction led to stent revascularization in patients with CAD [33]. Recent studies have also shown that baPWV was a significant predictor of CV events in patients with chronic CAD [30], and baPWV can be a risk stratification index for the short-term prognosis in clinical practice [34]. Ando *et al.* indicated that more lipid tissue was present in the neointima of

sirolimus-eluting stent (SES) than in BMS [35]. A focal angiographic pattern of restenosis was predominantly observed in the DES group. Neoatherosclerosis was responsible for ISR after DES implantation. Therefore, higher baPWV could be a predictor of TLR as the result of endothelial dysfunction and the progression of atherosclerosis in patients with CAD. Since DES implantation strongly prevented reendothelialization compared with BMS implantation, baPWV was only a predictor of MACE in patients with DES implantation, but not BMS implantation.

Furthermore, in patients with DES implantation, the use of insulin was a predictor of MACE, although there were no significant differences in the percentages of DM and oral hypoglycemic agents and HbA1c between patients with and without MACE. The progression of insulin resistance to diabetes parallels the progression of endothelial dysfunction to atherosclerosis [36]. Huang *et al.* demonstrated that high levels of insulin are potent at stimulating the proliferation of vascular smooth muscle [37]. On the other hand, some studies have suggested that insulin has opposite effects [38, 39]. Although the effects of insulin on atherosclerosis are controversial, the disadvantage of insulin may affect MACE in patients with DES implantation probably because DM patients with insulin generally have severe atherosclerosis in addition to endothelial dysfunction.

Overall, LVEF was significantly different between patients with and without MACE. Iijima *et al.* showed that lower LVEF was a predictor of restenosis in small vessels [40]. In fact, patients with MACE showed a smaller stent size than patients without MACE. Therefore, a lower LVEF was the result of severe ischemic heart disease, and consequently LVEF may be significantly associated with MACE in all patients.

Study limitations

This study has several limitations. First, the study was retrospective and included a relatively small number of patients. Second, non-invasive measurements were performed after various treatments. Many of the patients were taking anti-hypertensive, anti-dyslipidemic and/or anti-diabetic medications that may have influenced the measurements of the differences in BP between arms and baPWV. Third, we used 3 kinds of DES (SES, paclitaxel-eluting and biolimus-eluting stents). Fourth, we did not include some variables in a logistic regression analysis (chronic kidney disease, metabolic syndrome, and family history are known to be important factors in CV events). Longer, larger and prospective studies are needed to clarify these limitations.

Conclusion

Both relative difference in SBP between arms and baPWV were predictors of MACE after DES implantation, but not BMS implantation.

5. Conflict(s) of Interest/Disclosure(s)

K.S. is a Chief Director and S.M. is a Director of NPO Clinical and Applied Science, Fukuoka, Japan. K.S. has an Endowed Department of “Department of Molecular Cardiovascular Therapeutics” supported by MSD, Co. LTD. S.M. belongs to the Department of Molecular Cardiovascular Therapeutics supported by MSD, Co. LTD.

6. References

1. Amar J, Ruidavets JB, Chamontin B, Drouet L. Arterial stiffness and cardiovascular risk factors in a population-based study. J Hypertens 2001;19:381-389.
2. Arnett DK, Evans GW, Riley WA. Arterial stiffness: a new cardiovascular risk factor? Am J Epidemiol 1994;140: 669-682.
3. van Popele NM, Grobbee DE, Bots ML, Asmar R, Topouchian J, Reneman RS, Hoeks AP, van der Kuip DA, Hofman A, Witteman JC. Association between arterial stiffness and atherosclerosis. The Rotterdam study. Stroke 2001; 32:454-460.
4. Kawai T, Ohishi M, Takeya Y, Onishi M, Ito N, Oguro R, Yamamoto K, Kamide K, Rakugi H. Carotid plaque score and intima media thickness as predictors of stroke and mortality in hypertensive patients. Hypertens Res 2013;36:902-909.
5. Yamashina A, Tomiyama H, Takeda K, Tsuda H, Arai T, Hirose K, Koji Y, Hori S, Yamamoto Y. Validity, reproducibility, and clinical significance of noninvasive brachial-ankle pulse wave velocity measurement. Hypertens Res 2002;25:359-364.
6. Munakata M, Konno S, Miura Y, Yoshinaga K; J-TOPP Study Group. Prognostic significance of the brachial-ankle pulse wave velocity in patients with essential hypertension: final results of the J-TOPP study. Hypertens Res 2012;35:839-842.
7. Yoshida M, Mita T, Yamamoto R, Shimizu T, Ikeda F, Ohmura C, Kanazawa A, Hirose T, Kawamori R, Watada H. Combination of the Framingham risk score and carotid intima-media thickness improves the prediction of cardiovascular events in patients with type 2 diabetes. Diabetes Care 2012;35:178-180.
8. Tomiyama H, Koji Y, Yambe M, Shiina K, Motobe K, Yamada J, Shido N, Tanaka N, Chikamori T, Yamashina A. Brachial-ankle pulse wave velocity is a simple and independent predictor of prognosis in patients with acute coronary syndrome. Circ J 2005;69:815-822.
9. Laurent S, Boutouyrie P, Asmar R, Gautier I, Laloux B, Guize L, Ducimetiere P, Benetos A. Aortic stiffness is an independent predictor of all cause and

cardiovascular mortality in hypertensive patients. Hypertension 2001; 37:1236-1241.
10. Guerin AP, Blacher J, Pannier B, Marchais SJ, Safar ME, London GM. Impact of aortic stiffness attenuation on survival of patients in end-stage renal failure. Circulation 2001;103:987-992.
11. Clark CE, Taylor RS, Shore AC, Ukoumunne OC, Campbell JL. Association of a difference in systolic blood pressure between arms with vascular disease and mortality: a systematic review and meta-analysis. Lancet 2012;10:905-914.
12. Okada H, Fukui M, Tanaka M, Matsumoto S, Mineoka Y, Nakanishi N, Asano M, Yamazaki M, Hasegawa G, Nakamura N. A difference in systolic blood pressure between arms and between lower limbs is a novel risk marker for diabetic nephropathy in patients with type 2 diabetes. Hypertens Res 2013;36:403-407.
13. Simsek C, Onuma Y, Magro M, de Boer S, Battes L, van Domburg RT, Boersma E, Serruys PW; Interventional Cardiologists of the Thoraxcenter (2000-2005). Four-year clinical outcome of sirolimus- and paclitaxel-eluting stents compared to bare-metal stents for the percutaneous treatment of stable coronary artery disease. Catether cardiovasc interv 2010;76:41-49.
14. Kaiser C, Galatius S, Erne P, Eberli F, Alber H, Rickli H, Pedrazzini G, Hornig B, Bertel O, Bonetti P, De Servi S, Brunner-La Rocca HP, Ricard I, Pfisterer M; BASKET–PROVE Study Group. Drug-eluting versus bare-metal stents in large coronary arteries. N Engl J Med 2010;363:2310-2319.
15. Valgimigli M, Tebaldi M, Borghesi M, Vranckx P, Campo G, Tumscitz C, Cangiano E, Minarelli M, Scalone A, Cavazza C, Marchesini J, Parrinello G; PRODIGY Investigators. Two-year outcomes after first- or second-generation drug-eluting or bare-metal stent implantation in all-comer patients undergoing percutaneous coronary intervention : a pre-specified analysis from the PRODIGY study. JACC Cardiovasc Interv 2014;7:20-28.
16. Asmar R, Benetos A, Topouchian J, Laurent P, Pannier B, Brisac AM, Target R, Levy BI. Assessment of arterial distensibility by automatic pulse wave velocity measurement. Validation and clinical application studies. Hypertension 1995;26:485-490.
17. Shah A, Gnoj J, Fisher VJ. Complications of selevtive coronary arteriography by the Judkins technique and their prevention. Am Heart J 1975;90:353-359.
18. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, McGoon DC, Murphy ML, Roe BB. Areprting system on patients evaluated for coronary artery disease: report of the Ad Hoc Committee for Grading of Coronary Artert Disease, Council on Cardiovascular Surgery, American Heart Association. Circulation 1975;51: 5-40.
19. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E,Lansky A, Hamon M, Krucoff MW, Serruys PW; Academic Research Consortium. Clinical end points in coronary stent trials: a case of standardized definitions. Circulation 2007;115:2344-2351.
20. Chan CY, Vlachos H, Selzer F, Mulukutla SR, Marroquin OC, Abbott DJ, Holper EM, Williams DO. Comparison of drug-eluting and bare metal stents in large coronary arteries : Findings from the NHLBI dynamic registry. Catheter Cardiovasc Interv. 2013. in press.
21. Kasaoka S, Tobis JM, Akiyama T, Reimers B, Di Mario C, Wong ND, Colombo A. Angiographic and intravascular ultrasound predictors of in-stent restenosis. J Am Coll Cardiol 1998;32:1630-1635.
22. Pfisterer M, Brunner-La Rocca HP, Rickenbacher P, Hunziker P, Mueller C, Nietlispach F, Leibundgut G, Bader F, Kaiser C; BASKET. Long-term benefit-risk balance of drug-eluting vs. bare-metal stents in daily practice:does stent diameter matter? Three-year follow-up of BASKET. Eur Heart J 2009;30:16-24.
23. Lane D, Beevers M, Barnes N, Bourne J, John A, Malins S, Beevers DG. Inter-arm differences in blood pressure: when are they clinically significant? J Hypertens 2002;20:1089-1095.
24. Grossman A, Prokupetz A, Gordon B, Morag-Koren N, Grossman E. Inter-arm blood pressure differences in young, healthy patients. J Clin Hypertens 2013;15:575-578.
25. Cassidy P, Jones K. A study of inter-arm blood pressure differences in primary care. J Human Hypertens 2001;15:519-522.
26. Clark CE, Campbell JL, Evans PH, Millward A. Prevalence and clinical implications of the inter-arm blood pressure difference: A systematic review. J Human Hypertens 2006;20:923-931.
27. Eguchi K, Yacoub M, Jhalani J, Gerin W, Schwartz JE, Pickering TG. Consistency of blood pressure differences between the left and right arms. Arch Intern Med 2007;167:388-393.
28. Kimura A, Hashimoto J, Watabe D, Takahashi H, Ohkubo T, et al. Patient characteristics and factors associated with inter-arm difference of blood pressure measurements in a general population in ohasama, Japan. J Hypertens. 2004; 22:2277-2283.
29. Clark CE, Steele AM, Taylor RS, Shore AC, Ukoumunne OC, Campbell JL. Interarm blood pressure difference in people with diabetes: Measurement and vascular and mortality implications: A cohort study. Diabetes Care 2014. in press.
30. Sugamata W, Nakamura T, Uematsu M, Kitta Y, Fujioka D, Saito Y, Kawabata KI, Obata JE, Watanabe Y, Watanabe K, Kugiyama K. The combined assessment of flow-medicated dilation of the brachial artery and

brachial-ankle pulse wave velocity improves the prediction of future coronary events in patients with chronic coronary artery disease. J Cardiol 2014. in press.
31. Liu DH, Wang Y, Liao XX, Xu MG, Wang JM, Yang Z, Chen L, Lü MD, Lu K, Tao J. Increased brachial-ankle pulse wave velocity is associated with impaired endothelial function in patients with coronary artery disease. Chin Med J 2006;119:1866-1870.
32. Xiong Z, Zhu C, Zheng Z, Wang M, Wu Z, Chen L, Chen Y. Relationship between arterial stiffness assessed by brachial ankle pulse wave velocity and coronary artery disease severity assessed by the SYNTAX score. J Atheroscler Thromb 2012;19:970-976
33. Munk PS, Butt N, Larsen AI. Endothelial dysfunction predicts clinical restenosis after percutaneous coronary intervention. Scand Cardiovasc J 2011;45:139-145.
34. Nakamura M, Yamashita T, Yajima J, Oikawa Y, Sagara K, Koike A, Kirigaya H, Nagashima K, Sawada H, Aizawa T; Shinken Database Study Group. Brachial-ankle pulse wave velocity as a risk stratification index for the short-term prognosis of type 2 diabetic patients with coronary artery disease. Hypertens Res 2010;33:1018-1024.
35. Ando H, Amano T, Takashima H, Harada K, Kitagawa K, Suzuki A, Kunimura A, Shimbo Y, Harada K, Yoshida T, Kato B, Uetani T, Kato M, Matsubara T, Kumagai S, Yoshikawa D, Isobe S, Ishii H, Murohara T. Differences in tissue characterization of restenotic neointima between sirolimus-eluting stent and bare-metal stent: integrated backscatter intravascular ultrasound analysis for in-stent restenosis. Eur Heart J Cardiovasc Imaging 2013;14:996-1001.
36. Hadi H, Suwaidi J. Endothelial dysfunction in diabetes mellitus. Vasc Health Risk Manag 2007;3:853-876.
37. Huang B, Dreyer T, Heidt M, Yu JC, Philipp M, Hehrlein FW, Katz N, Al-Fakhri N. Insulin and local growth factor PDGF induce intimal hyperplasia in bypass graft culture models of saphenous vein and internal mammary artery. Eur J Cardiothorac Surg 2002;21:1002-1008.
38. Vehkavaara S, Yki-Järvinen H. 3.5 years of insulin therapy with insulin glargine improves in vivo endothelial function in type 2 diabetes. Arterioscler Thromb Vasc Biol 2004;24:325-330.
39. Dandona P, Chaudhuri A, Mohanty P, Ghanim H. Anti-inflammatory effects of insulin. Curr Opin Clin Nutr Metab Care 2007;10:511-517.
40. Raisuke I, Yuji I, Akiyoshi M, Hiroyoshi N, Kazuhiro H. Predictors of restenosis after implantation of 2.5 mm stents in small coronary arteries. Circ J 2004;68: 236-240.