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Original article

Low ankle brachial index predicts poor outcomes including target lesion revascularization during the long-term follow up after drug-eluting stent implantation for coronary artery disease

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ABSTRACT

Background: Peripheral arterial disease (PAD) frequently coexists with coronary artery disease (CAD). The ankle-brachial index (ABI) is widely used for the screening for PAD. Low ABI is associated with short-term clinical outcomes in patients receiving coronary drug-eluting stent (DES) implantation. However, there is no report to examine the relationship between lower ABI and long-term clinical outcomes after DES implantation. Thus, we investigated the clinical long-term impact of low ABI after DES implantation.
Methods: This retrospective analysis included 181 CAD patients treated with DES from April 2010 to March 2013 in our institute. Based on ABI values, we divided the subjects into the low-ABI group($ABI < 0.9$, $n = 29$) and the normal ABI group($0.9 \leq ABI < 1.4$, $n = 152$). The incidence of target lesion revascularization (TLR), all-cause mortality, and major adverse cardiac and cerebrovascular events (MACCE) defined as a composite of cardiac death, myocardial infarction, stroke, and any repeat revascularization, were compared between the 2 groups.
Results: During the median follow-up period of 43 months, the incidences of TLR, all-cause mortality, and MACCE were significantly higher in the low ABI group than in the normal ABI group (TLR: 41.4% vs 9.9%, $p < 0.001$, all-cause mortality: 31.0% vs 3.9%, $p < 0.001$, MACCE: 48.3% vs 11.2%, $p < 0.001$, respectively).
Conclusions: Low ABI may predict poor long-term outcomes, including TLR, in CAD patients treated with DES.

Introduction

Drug-eluting stents (DES) have dramatically reduced the rate of in-stent restenosis and target lesion revascularization (TLR) after percutaneous coronary intervention (PCI) as compared with bare-metal stents [1–4]. Despite the significant advances in the DES technology, restenosis requiring TLR cannot be completely eliminated even in the DES era. The underlying mechanisms of restenosis with DES can be attributable to several factors, such as patient, arterial, stent, and procedural factors [5].

Peripheral arterial disease (PAD) is a manifestation of progressive systemic atherosclerosis and patients with PAD frequently have concomitant coronary artery disease (CAD) [6]. The ankle-brachial index (ABI) is widely used as a diagnostic tool for screening for PAD. As previously reported, low ABI has a poor prognosis [7–10]. In addition, lower ABI is associated with worse cardiac function [11], the severity of CAD [12,13], and moreover it is considered as an independent predictor of short-term clinical outcomes in patients who underwent PCI [14–16]. However, there is no report to examine the relationship between low ABI and long-term clinical outcomes after DES implantation.

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Thus, we investigated the clinical long-term impact of lower ABI in patients who underwent PCI with DES.

Methods

Study population

This was a retrospective observational, single-center study. A total of 547 patients with CAD received PCI in our center between April 2010 and March 2013, of those 407 patients were treated with DES. The patients who did not undergo ABI measurement during the follow up period, were excluded. We also excluded the patients who presented with ABI > 1.4. Finally, 181 patients were analyzed in this study.

All enrolled patients provided written informed consent and the design of this study was approved by the ethics committees of Kurume University School of Medicine (Certified number: 14035).

Data collection & follow up

We reviewed the medical records of enrolled patients and obtained the clinical data including patient demographic information, baseline clinical characteristics, cardiovascular risk factors, and angiographic characteristics. To ensure accurate assessment of clinical outcomes, additional information was obtained from visits, medical records, or telephone contacts with living patients or family members.

Definitions

Hypertension was diagnosed as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, or having been treated for hypertension. Dyslipidemia was defined as serum low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, triglycerides ≥150 mg/dL, or having been treated for dyslipidemia. In addition, LDL-C ≥ 100 mg/dL after PCI was defined as dyslipidemia in this study. Diabetes mellitus was defined as fasting plasma glucose levels ≥126 mg/dL with hemoglobin A1c (HbA1c) levels ≥6.5%, random glucose level ≥200 mg/dL with HbA1c ≥6.5%, or having been treated with insulin and/or an oral hypoglycemic agent. Chronic kidney disease was defined as estimated creatinine clearance <30 mL/min.

ABI measurement

The ABI measurements were performed in each patient prior to PCI. In each patient, blood pressure was measured in the brachial arteries and in the dorsalis pedis and the posterior tibial arteries, using a Doppler device (BP-203RPEIII, Fukuda Colin, Tokyo, Japan). The ABI is a ratio between the ankle systolic blood pressure and the brachial systolic blood pressure. If the ABI resulted in abnormal value (<0.90 or >1.40), measurements were repeated in the same situation. The lower ABI values for the left and right legs were adopted as the ABI.

Clinical outcomes

The primary outcome of this study was the incidence of TLR after PCI. TLR was performed based on the following: (1) angiographical severe restenosis (≥90% stenosis according to the American Heart Association classification); (2) ischemic evidence of functional ischemia evaluation including treadmill exercise test, stress myocardial scintigraphy, or fractional flow reserve assessment. All subjects underwent follow-up coronary angiography about 9 months after PCI when the consent was obtained. In addition to the follow-up coronary angiography, if the patients had ischemic evidence such as chest pain and abnormal test results, they underwent PCI as necessary. The secondary outcomes were all-cause mortality, and the major adverse cardiac and cerebrovascular events (MACCE) defined as a composite of cardiac death, myocardial infarction (MI), stroke, and any repeat revascularization. MI was defined as the development of significant Q waves on electrocardiogram or creatine kinase rise of at least twice the upper normal limit (<248 U/L). Stroke included brain hemorrhage and cerebral infarction. Repeat revascularization was a composite of target and non-target vessel revascularization treated with PCI or coronary artery bypass graft surgery. The final survey was performed in March 2015.

Statistical analysis

All continuous variables were given as the mean ± standard deviation or median with interquartile range. Categorical data were presented as number (n) or percentage (%). For intergroup comparisons, an unpaired t-test was applied in continuous variables, and chi-square test or Fisher exact test was used in categorical variables. Cumulative incidences were estimated using Kaplan-Meier method and compared by the log-rank test. To reduce the confounding effects, we adopted Cox proportional hazard model for significant differences in the baseline characteristics. All statistical analyses were performed with the SAS software program (version 9.3, SAS Institute, Cary, NC, USA). All tests were two-tailed and p-values of <0.05 were considered statistically significant.

Results

The distribution of ABI in this study is illustrated in Fig. 1. Based on the ABI value, the subjects were divided into 2 groups; 16% (n = 29) in the low ABI group (ABI < 0.9) and 84% (n = 152) in the normal ABI group (0.9 ≤ ABI < 1.4). The median follow-up period was 45 (interquartile range 34–55) months in the low ABI group and 42 (interquartile range 34–49) months in the normal ABI group. The patient characteristics of the study population according to the ABI are shown in Table 1. Patients in the low ABI group were significantly older and had a significantly higher prevalence of diabetes, chronic kidney disease, and history of PCI than the normal ABI group. Severity of CAD in patients is summarized in Table 2. The prevalence of multivessel disease was higher in the low ABI group than in the normal ABI group.

Clinical outcomes

Clinical outcomes are shown in Table 3 and Fig. 2. During the follow-up period, all-cause death events occurred in 15 patients. Details of the death events are presented in **Supplementary** Table 1. The incidence of TLR, all-cause mortality, and MACCE was significantly higher in the low ABI group than in the normal ABI group (TLR: 41.4% vs 9.9%, $p < 0.001$, all-cause mortality: 31.0% vs 3.9%, $p < 0.001$, MACCE: 48.3% vs 11.2%, $p < 0.001$, respectively). After multivariable adjustment, the low ABI group had significantly higher rates of TLR [hazard ratio (HR), 5.28, 95% confidence interval (CI), 1.61–17.33, $p = 0.006$] and MACCE (HR, 5.04. 95% CI, 1.82–13.98, $p = 0.002$) than the normal ABI group. However, all-cause mortality was not significantly different between the two groups (HR, 3.71. 95% CI, 0.89–15.45, $p = 0.07$).

Discussion

The present study evaluated the impact of low ABI on TLR over 3.5 years in the patients undergoing PCI with DES. The results of this study have demonstrated that low ABI is significantly associated with increased risk of TLR and MACCE even after adjustment for various confounding factors.

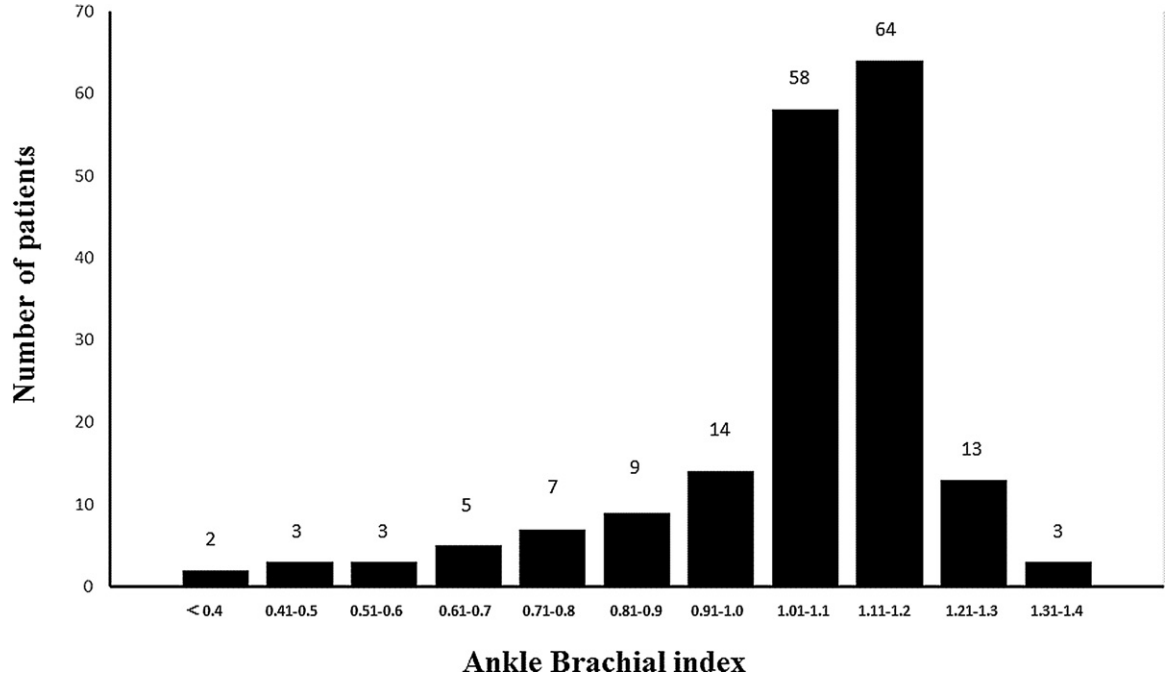

Fig. 1. Distribution of lower side ankle brachial index in all patients.

Table 1
Patient characteristics.

	Low ABI ($n=29$)		Normal ABI ($n=152$)		p-value
Age (years)	72.9	±7.4	69.1	±8.9	0.030
Sex (female)	8	27.6%	43	28.3%	0.938
ABI (low side)	0.71	±0.13	1.12	±0.08	<0.001
Hypertension	26	89.7%	123	80.9%	0.259
Dyslipidemia	24	82.8%	139	91.5%	0.152
Diabetes mellitus	20	68.9%	67	44.1%	0.014
Smoking	13	44.8%	58	38.2%	0.500
CKD (Ccr < 30 ml/min) (Hemodialysis)	9 (7)	31.0% (24.1%)	8 (5)	5.3% (3.3%)	<0.001 (<0.001)
Old myocardial infarction	8	27.6%	44	28.9%	0.882
PCI history before registration	11	37.9%	22	14.5%	0.003
Acute coronary syndrome	7	24.1%	22	14.5%	0.194
Multi vessel disease	11	37.9	49	32.2	0.551
Coronary artery bypass grafting	3	10.3%	5	3.3%	0.090
Stroke history	2	6.9%	11	7.2%	0.948
Revascularization for PAD	15	51.7%	0	0%	<0.001
Medication at follow up					
Aspirin	28	96.6%	148	97.4%	0.806
Clopidogrel	28	96.6%	145	95.4%	0.781
Statin	24	82.8%	139	91.5%	0.152
ACE-I or ARB	23	79.3%	121	79.6%	0.971
Calcium antagonist	19	65.5%	71	46.7%	0.063
Beta-blocker	13	44.8%	78	51.3%	0.522

Values are mean ± standard deviation or n (%).
ABI, ankle brachial index; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; Ccr, creatinine clearance; CKD, chronic kidney disease; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

Previous studies have shown that low ABI indicates worse clinical outcomes in several types of patients such as the general population, and those with peripheral artery disease and acute coronary syndrome. However, there have been a few studies investigating association between low ABI and clinical outcomes after DES deployment. Ribera et al. demonstrated that abnormal ABI value (≤0.9 or ≥1.4) is related with fatal outcomes, but not with revascularizations in patients receiving DES implantation during 1 year follow up [16]. Similarly, Kim et al. reported that lower ABI is associated with poor cardiovascular outcomes in patients with DES implantation during about 10 months of follow up [17]. Our findings are similar to these findings, particularly we found that the low ABI group had a higher incidence of TLR with DES than the normal ABI group during the long-term follow-up.

Previous studies have reported that predictors of restenosis with DES are small vessel size, long stented length, complex lesion morphology, diabetes mellitus, chronic hemodialysis, and history of bypass surgery [18–20]. In this study, no significant differences were found in the total stented length and the prevalence of type B2/C lesion, small vessel lesion, and history of coronary artery bypass grafting surgery between the low and the normal ABI

Table 2
Lesion profile.

	Low ABI (48 lesions)		Normal ABI (229 lesions)		*p*-value
Type B2, C	38	79.2%	152	66.4%	0.083
Left main trunk	5	10.4%	21	9.2%	0.778
Left anterior descending artery	17	35.4%	107	46.7%	0.152
Left circumflex artery	9	18.2%	37	16.2%	0.661
Right coronary artery	17	35.4%	64	28.0%	0.301
Chronic total occlusion	4	8.3%	22	9.6%	0.783
Acute coronary syndrome	7	14.6%	26	11.4%	0.523
Revascularization lesion	10	20.8%	25	10.9%	0.055
Stent diameter (mm)	3.00	±0.38	3.02	±0.36	0.687
Stent length (mm)	32.31	±16.77	30.44	±15.56	0.448

ABI, ankle brachial index.

Table 3
Incidence of clinical outcomes according to the ABI.

			Unadjusted		Multivariable-adjusted[a]	
	Low ABI (*n* = 29)	Normal ABI (*n* = 152)	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Primary outcome						
TLR	12 (41.4%)	15 (9.9%)	6.45 (2.59–16.04)	<0.001	5.28 (1.61–17.33)	0.006
Secondary outcomes						
All-cause mortality	9 (31.0%)	6 (3.9%)	10.95 (3.52–34.03)	<0.001	3.71 (0.89–15.45)	0.07
MACCE	14 (48.3%)	17 (11.2%)	7.41 (3.06–18.98)	<0.001	5.04 (1.82–13.98)	0.002

ABI, ankle-brachial index; CI, confidence interval; HR, hazard ratio; MACCE, major adverse cardiac and cerebrovascular events; TLR, target lesion revascularization.
[a] Adjusted for age, diabetes mellitus, chronic kidney disease, history of percutaneous coronary intervention, and triple vessel disease.

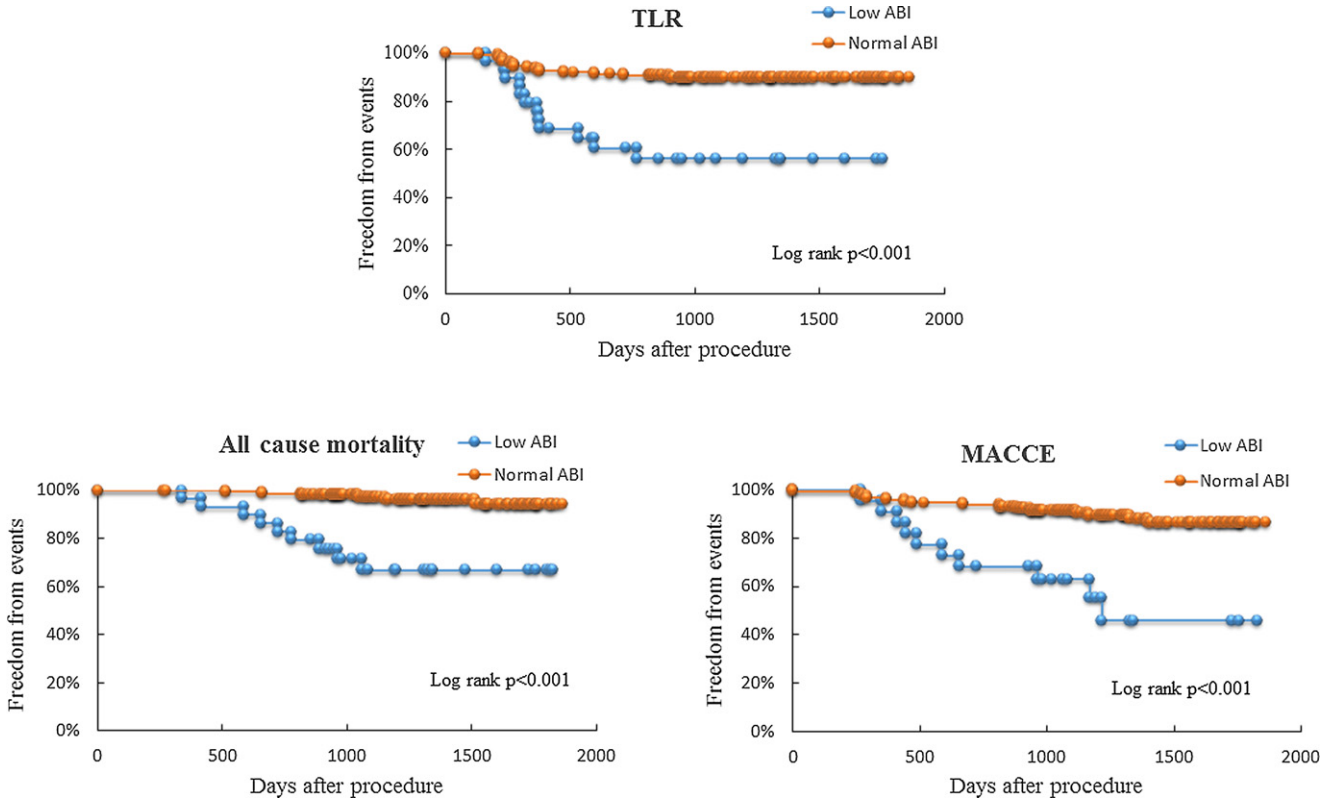

Fig. 2. Primary and secondary outcome events.
ABI, ankle brachial index; MACCE, major adverse cardiac and cerebrovascular events; TLR, target lesion revascularization.

group, however, the low ABI group significantly had a higher incidence of diabetes mellitus and triple vessel disease than the normal ABI group. But, significant differences in the rate of TLR and MACCE were still observed after adjusting for multiple factors. Therefore, our findings suggested that low ABI was an independent risk factor of TLR after DES implantation.

Presence of PAD is a marker of systemic atherosclerosis that stems from vascular endothelial dysfunction. CAD patients with

PAD have higher circulating levels of inflammatory and prothrombotic biomarkers [21,22]. In addition, other reports have shown that some markers of oxidative stress were associated with PAD [23,24]. These pathways might play an important role in accelerating atherosclerotic disease progression in PAD patients. However, this area clearly requires further investigation.

Several limitations of the present study should be noted. First, this study was a relatively small, retrospective, single-center study. Nakahashi et al. demonstrated that low ABI is significantly associated with an increased risk of long-term all-cause mortality in larger sample size of patients with acute coronary syndrome [25]. In contrast, the current study showed that a statistically significant difference was not found in all-cause mortality after multivariable adjustment although a statistical trend remained. The sample size of this study could affect the current results. Second, ABI measurement was not a routine test among patients with CAD in our hospital. Therefore, a relatively large number of patients who did not undergo ABI measurement was excluded in this study. Third, although the patients of high ABI (>1.4) were excluded, we included the borderline ABI patients (0.91-0.99) in the normal ABI group because of a small sample size. Finally, not all confounders were controlled for in the multivariable analysis.

Conclusions

Our findings suggest that a low ABI was an independent risk factor of poor outcomes, including TLR, in CAD patients treated with DES. Measuring ABI is a simple and noninvasive method and may have the potential benefit of predicting future events in patients receiving DES.

Disclosures

All authors have no conflict of interest to disclose.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jjcc.2019.07.015.

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