

Prognostic Value of Ankle-Brachial Index in Patients Undergoing Percutaneous Coronary Intervention: In-Hospital and 1 Year Outcomes from the SHINANO Registry

Naoto Hashizume, MD<sup>1</sup>, Takashi Miura, PhD<sup>1</sup>, Yusuke Miyashita, PhD<sup>2</sup>, Hirohiko Motoki, PhD<sup>1</sup>, Soichiro Ebisawa, PhD<sup>1</sup>, Atsushi Izawa, PhD<sup>1</sup>, Jun Koyama, PhD<sup>1</sup>, Uichi Ikeda, PhD<sup>1</sup>, and Koichiro Kuwahara, PhD<sup>1</sup>; SHINANO Registry Investigators.

<sup>1</sup>Department of Cardiovascular Medicine, Shinshu University School of Medicine, Matsumoto, Japan; <sup>2</sup>Department of Cardiology, Nagano Red Cross Hospital, Nagano, Japan.

Institution where work was performed: Department of Cardiovascular Medicine, Shinshu University School of Medicine, Matsumoto, Japan.

Address for Correspondence: Naoto Hashizume, MD, Department of Cardiovascular Medicine, Shinshu University School of Medicine. 3-1-1 Asahi, Matsumoto, Japan. Zip code: 390-8621. Tel: +81-263-37-3352; Fax: +81-263-37-2573. E-mail address: hashy0804@yahoo.co.jp

E-mail addresses for co-authors: T. Miura, miuramen10miuramen@yahoo.co.jp; Y. Miyashita, ybm1965@yahoo.co.jp; H. Motoki, hmotoki@shinshu-u.ac.jp; S. Ebisawa, ebisawa@shinshu-u.ac.jp; A. Izawa, izawa611@shinshu-u.ac.jp; J. Koyama, jkoyama@shinshu-u.ac.jp; U. Ikeda, uikeda@shinshu-u.ac.jp; K. Kuwahara, kkuwah@shinshu-u.ac.jp.

Hashidume et al. Prognostic Value of Ankle-Brachial Index

This paper was presented orally at the American College of Cardiology 65th Annual Scientific Session, April 3, 2016, in Chicago, Illinois, USA.

**Abstract**

Concomitant coronary and peripheral artery disease are associated with higher periprocedural and long-term percutaneous coronary intervention (PCI) complication rates. We evaluated in-hospital and 1-year clinical outcomes of patients with low or borderline ankle-brachial indexes (ABIs) undergoing PCIs in the drug-eluting stent era. We divided 1,370 SHINANO registry patients into 3 groups: low ( $ABI \leq 0.9$ ), borderline ( $0.9 < ABI \leq 1.0$ ), and normal ( $1.0 \leq ABI < 1.4$ ). During 1-year of follow-up, more PCI-related complications occurred in the low and borderline ABI groups than in the normal ABI group (7.7 vs 8.8 vs 4.0%, respectively). Low ABI patients were more likely to experience adverse clinical events (6.3 vs 3.6 vs 3.0%, respectively; log-rank  $p = 0.020$  for low vs normal ABI), with a hazard ratio 2.27 (95% confidence interval, 1.12-4.61;  $p = 0.023$ ), compared with patients with normal ABIs. Patients with abnormal ABIs had a significantly higher incidence of PCI-related complications and a less favorable 1-year prognosis. Routine ABI measurement before PCI may help predict PCI-related complication incidence and 1-year prognosis.

**Key words:** ankle-brachial index, percutaneous coronary intervention, complications, prognosis.

## Introduction

Atherosclerosis is a systemic disease that affects coronary, cerebral, and lower-extremity arteries and is associated with the primary worldwide cause of mortality.<sup>1</sup> Patients with peripheral artery disease (PAD), have a poor long-term prognosis, regardless of whether they are symptomatic.<sup>2</sup> Although the prevalence of asymptomatic PAD is high in patients with cardiovascular (CV) risk factors, a considerable number of patients with PAD remain undiagnosed.<sup>3</sup>

The ankle-brachial index (ABI) has become the gold standard for PAD detection, because of its simplicity, reproducibility and cost-effectiveness.<sup>4</sup> ABI measurements  $\leq 0.90$  and 0.90-0.99 can identify patients with definite and borderline PAD, respectively. Patients with even borderline PAD may be at increased risk of subsequent cardiovascular events.<sup>5,6</sup> Thus, ABI measurement may help to identify asymptomatic individuals with CV risk.<sup>7</sup>

Patients with coronary artery disease (CAD) generally receive percutaneous coronary intervention (PCI). In recent years, PCI has become safer and less invasive owing to the development of devices and approaches, such as the trans-radial approach and slender PCI.<sup>8,9</sup> Although drug-eluting stents (DES) markedly reduce the rates of target-lesion revascularization,<sup>10</sup> the safety of discontinuing dual antiplatelet therapy remains controversial in terms of late or very late stent thrombosis even after the advent of second-generation DES.<sup>11</sup>

In fact, more than half of the patients with PAD have concomitant CAD.<sup>12,13</sup> Patients with concomitant CAD and PAD who underwent PCI had higher periprocedural and long-term complications than those without PAD in the era of the bare-metal stent;<sup>14,15</sup> however, the clinical outcomes of patients with definite or borderline PAD have not been systematically studied in the era of the DES. Therefore, we evaluated the in-hospital and

1-year clinical outcomes of patients with definite or borderline PAD who underwent PCI in the DES era.

## **Materials and Methods**

### *Study population*

The study protocol was developed in accordance with the Declaration of Helsinki and was approved by the ethics committee of each participating institution. All patients gave written informed consent before participating in this study. This retrospective cohort study used data obtained from the Shinshu Prospective Multi-center Analysis for Elderly Patients with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention (SHINANO) registry, the details of which have been published previously.<sup>16</sup> Briefly, the SHINANO registry is a prospective, multicenter, observational registry designed to compare differences in baseline characteristics and short-term and long-term outcomes after initial PCI between elderly and non-elderly patients. Between August 2012 and July 2013, a total of 1,923 consecutive patients with all forms of CAD (stable angina, ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and unstable angina) were enrolled from 16 institutions located in the Nagano prefecture of Japan. This registry applied no exclusion criteria. It was registered with the University Hospital Medical Information Network Clinical Trials Registry, which is accepted by the International Committee of Medical Journal Editors (No. UMIN000010070).

For the current sub-analysis, we identified 1,370 patients in whom ABIs were measured, and divided them into 3 groups according to the 2011 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) guideline classification:<sup>17</sup> low ABI (n = 209;  $ABI \leq 0.9$ ), borderline ABI (n = 171;  $0.9 < ABI \leq 1.0$ ) and normal ABI (n = 990;  $1.0 \leq$

ABI < 1.4). Patients with values indicating non-compressible arteries (i.e. ABI > 1.4) in either limb were excluded. The ABI was measured with subjects in the supine position after at least 5 min of rest using an automatic oscillometric apparatus according to the recommendations of the AHA.<sup>18</sup> The ABI was calculated separately for each leg, and the lower of the two values was used for analysis. Patients were prospectively followed up for 1 year (Figure 1).

The in-hospital endpoint was the incidence of PCI-related complications, including periprocedural myocardial infarction, periprocedural stroke, coronary perforation, bleeding complications, contrast-induced nephropathy, and cholesterol crystal embolization. The 1-year endpoint was net adverse clinical events (NACE), defined as the combined incidence of CV death, nonfatal myocardial infarction, ischemic or hemorrhagic strokes, and major bleeding at 1 year after hospital discharge.

### *Definitions*

Periprocedural myocardial infarction was defined as a creatine kinase or creatine kinase-MB fraction above the upper limit of normal at each hospital or as the development of significant Q waves in at least two contiguous electrocardiogram leads. Periprocedural stroke was defined as a non-hemorrhagic stroke or transient ischemic attack related to PCI in the absence of other causes. A consultant neurologist evaluated all patients experiencing ischemic strokes after PCI.<sup>19</sup> Bleeding complications were defined as blood transfusions or prolonged hospitalization owing to hematoma, gastrointestinal bleeding, or intracranial bleeding. Contrast-induced nephropathy was defined as an increase in the serum creatinine level of 25% or an increase of 0.5 mg/dL from baseline within 72 h of contrast exposure. CV death was defined as any death due to an immediate cardiac or vascular cause, such as fatal myocardial infarction, ischemic or hemorrhagic stroke, aortic dissection, aneurysm rupture,

gastro-intestinal hemorrhage, or unexpected sudden death. Documented PAD consisted of one or both of the following criteria: current intermittent claudication with an ABI  $\leq 0.9$  or a history of intermittent claudication with a previous related intervention.

### *Statistical analysis*

Continuous variables are presented as mean (standard deviation), and binary variables are described as numbers and percentages. Differences between ABI groups were compared using the Kruskal–Wallis test for continuous variables and Pearson’s chi-square test for categorical variables. The landmark analysis was performed in accordance with a landmark point at hospital discharge, with the hazard ratio calculated for events that occurred between discharge and the end of the follow-up period. The Kaplan-Meier test was performed to assess the cumulative incidence of NACE, and the log-rank test was used to compare survival curves. A multivariate Cox regression analysis was performed to determine the independent predictors of NACE in the study population. A two-tailed  $p < 0.05$  was considered significant. Statistical analysis was performed using the Statistical Package for Social Sciences version 21 for Windows (SPSS Inc., Chicago, IL).

## **Results**

### *Baseline demographics and lesion characteristics*

Patient and lesion characteristics are shown in Tables 1 and 2, respectively. The prevalence of low, borderline, and normal ABI values was 15.3% ( $n = 209$ ), 12.5% ( $n = 171$ ) and 72.3% ( $n = 990$ ), respectively. In the low ABI group, 57.7% of patients were diagnosed with PAD before receiving PCI. ABI values decreased with older age and increasing leanness in patients. There were significantly more female patients in the low and borderline ABI groups, and they

had more comorbid conditions, including diabetes, atrial fibrillation, and renal dysfunction. Only anticoagulants, statins, and insulin use were significantly different between groups at discharge, which could reflect patient characteristics. Compared with patients with normal ABIs, patients with low and borderline ABIs had more complex lesions, including multivessel disease, diffuse lesions, left main trunk disease, ostial lesions, and calcified lesions requiring rotational atherectomy. The SYNTAX score was significantly higher, and the rate of using a trans-radial approach was significantly lower in these patients, reflecting lesion complexity. Although the rate of DES use was comparable across the groups, the rate of continued dual antiplatelet therapy tended to be higher in the low and borderline ABI groups than in the normal ABI group.

#### *PCI-related complications*

Figure 2 shows the incidence of PCI-related complications during hospitalization. Compared with patients with normal ABIs, patients with low and borderline ABIs tended to experience more frequent periprocedural strokes (1.0 vs 1.8 vs 0.3% for low ABI, borderline ABI, and normal ABI groups, respectively;  $p = 0.183$  for low ABI,  $p = 0.014$  for borderline ABI, vs normal ABI, respectively), as well as contrast-induced nephropathy (1.9 vs 2.9 vs 0.8%, respectively;  $p = 0.145$ ,  $p = 0.015$ , vs normal ABI, respectively). There were no significant differences between groups in terms of the rates of periprocedural myocardial infarction (2.4 vs 2.9 vs 1.5%, respectively;  $p = 0.368$ ,  $p = 0.191$ , vs normal ABI, respectively) or bleeding complications (1.9 vs 1.2 vs 1.1%, respectively;  $p = 0.343$ ,  $p = 0.945$ , vs normal ABI, respectively). Overall, patients with low and borderline ABIs had a significantly higher incidence of PCI-related complications than did patients with normal ABIs (7.7 vs 8.8 vs 4.0%, respectively;  $p = 0.024$ ,  $p = 0.017$ , vs normal ABI, respectively). In addition, multiple



logistic regression analysis revealed that low and borderline ABIs were independent predictors of PCI-related complications, even after adjustment for conventional confounding factors, including age, sex, hypertension, current smoking, dyslipidemia, and diabetes (odds ratio [OR]: 1.94, 95% confidence interval [CI]: 1.07-3.54,  $p = 0.030$  for low ABI and OR: 1.91, 95% CI: 1.01-3.63,  $p = 0.048$  for borderline ABI). Nevertheless, these findings were not significant after adjusting for SYNTAX score (OR: 1.72, 95% CI: 0.92-3.21,  $p = 0.089$  for low ABI and OR: 1.60, 95% CI: 0.77-3.31,  $p = 0.208$  for borderline ABI).

#### *Clinical outcomes during the 1-year follow-up*

Figure 3 shows the Kaplan-Meier analysis for 1-year follow-up, and Table 3 presents the Cox proportional hazard regression analysis for NACE. Patients with low ABI had a significantly higher incidence of NACE (6.3 vs 3.6 vs 3.0%, for low ABI, borderline ABI, and normal ABI, respectively; log-rank  $p = 0.020$  for low vs normal ABI). After adjustment for conventional confounding factors, including age (quartiles), sex, current smoking, hypertension, dyslipidemia, and diabetes, low ABI remained an independent predictor of NACE (hazard risk [HR]: 2.27 95% CI: 1.12-4.61,  $p = 0.023$ ), CV death (HR: 4.94, 95% CI: 1.19-20.58,  $p = 0.028$ ), stroke (HR: 4.42, 95% CI: 1.14-17.15,  $p = 0.032$ ), and major bleeding (HR: 3.89, 95% CI: 1.28-11.82,  $p = 0.017$ ). Although patients with borderline ABI had an incidence of NACE comparable to that in controls (HR: 1.10, 95% CI: 0.45-2.68,  $p = 0.838$ ), they tended to experience CV death (HR: 3.51, 95% CI: 0.82-15.08,  $p = 0.091$ ) and major bleeding (HR: 3.21, 95% CI: 1.05-9.79,  $p = 0.041$ ) more frequently. Interestingly, hemorrhagic events occurred more frequently in the low and borderline groups. In the breakdown of all CV death events, the proportion of hemorrhage-related CV death in low and borderline ABI groups was significantly higher than that in the normal ABI group (50 vs 67 vs 20%, for low ABI,

borderline ABI, and normal ABI, respectively;  $p = 0.011$  for low ABI,  $p = 0.024$  for borderline ABI, *vs* normal ABI, respectively) (Figure 4A). Additionally, in the breakdown of all stroke events, intracerebral bleeding was involved in 40% in the low ABI group and 50% in the borderline ABI group, while all strokes in the normal ABI group were ischemic strokes ( $p = 0.002$  for low ABI,  $p = 0.156$  for borderline ABI, *vs* normal ABI, respectively) (Figure 4B).

## Discussion

The present results clearly demonstrate that low ABI was significantly associated with increased risk of PCI-related complications and 1-year CV events. In addition, a borderline ABI was associated with a higher risk of PCI-related complications; this relationship remained significant even after adjusting for potential confounding factors. Furthermore, hemorrhage-related CV death and intracerebral bleeding during the 1-year follow-up were more frequently reported in the low and borderline ABI group.

In a previous report from the bare metal stent era, Saw et al. presented a pooled analysis of 19,867 patients undergoing PCI.<sup>14</sup> Patients with PAD had a higher incidence of 7-day death (1.0 *vs* 0.4%;  $p < 0.001$ ), 7-day myocardial infarction (6.8 *vs* 5.6%;  $p = 0.047$ ) and 1-year death (5.0 *vs* 2.1%;  $p < 0.001$ ) than patients without PAD. Singh et al. analyzed the outcomes of 7,696 patients undergoing PCI and reported that patients with PAD had a higher incidence of in-hospital complications than did patients without PAD, including death (3 *vs* 1%, respectively;  $p < 0.001$ ), myocardial infarction (8 *vs* 5%, respectively;  $p < 0.001$ ), and blood-loss requiring transfusion (11 *vs* 6%, respectively;  $p < 0.001$ ).<sup>15</sup> Compared with previous reports, the current study showed that PCI is now safer than before, in terms of periprocedural myocardial infarction and major bleeding; however, the risk of PCI-related

complications and less favorable 1-year prognoses remain higher in PAD patients, despite recent developments in devices and techniques.

ABI is an easy and reliable tool for identifying patients with subclinical PAD and indicating generalized atherosclerosis.<sup>7,18</sup> An  $ABI \leq 0.90$  is significantly associated with an increased risk of all-cause and CV mortality.<sup>20-23</sup> Carvounis et al. have reported that 28% of patients with CV risks had asymptomatic PAD, defined as an  $ABI \leq 0.90$ .<sup>3</sup> In the present study, the subjects' mean age was  $70.4 \pm 11.0$  years, which is higher than that reported by Carvounis et al., and more than 40% of patients with low ABIs were not diagnosed with PAD before the PCI procedure. Routine ABI measurement may improve the prediction of PCI-related complications and 1-year prognosis.

#### *PCI-related complications*

In the present study, patients with low and borderline ABIs had significantly higher SYNTAX scores and experienced PCI-related complications more frequently than did patients with normal ABIs. Additionally, lesion complexity itself seemed to affect the incidence of PCI-related complications. Previously, Sebastianski et al. reported that patients with PAD were more likely to have high SYNTAX scores,<sup>24</sup> and Endo et al. reported that angiographic lesion complexity was associated with in-hospital mortality and complication rate.<sup>25</sup>

In our study, patients with low ABIs tended to experience more frequent bleeding complications, although this result was not statistically significant. Fewer patients with abnormal ABIs underwent PCI via a trans-radial approach. In addition, PCI operators may need to conduct PCIs through the trans-brachial approach in patients with low ABIs, due to atherosclerotic lesions in the iliac artery, or the necessity to avoid radial punctures in anticipation of future hemodialysis access; this approach could increase vascular access site

complications. Furthermore, complex lesions frequently require thicker guiding catheters, and the use of 7- and 8-Fr guides to perform PCI was associated with increased contrast volume, renal complications, bleeding, and vascular access site complications when compared with 6-Fr guides.<sup>26</sup>

Although the total incidence of periprocedural myocardial infarction in this study (1.8%) was less than that reported in previous reviews,<sup>27</sup> patients with low and borderline ABIs tended to experience this complication more frequently than patients with normal ABIs, although the difference was not statistically significant. An intravascular ultrasound study has shown a strong correlation between the atherosclerotic plaque burden and the incidence of periprocedural myocardial infarctions.<sup>28</sup> Patients with multivessel disease, multiple or long lesions, or diffusely diseased arteries have a larger atherosclerotic burden and are more prone to periprocedural myocardial infarction. Complex lesions requiring complex PCIs predispose patients to periprocedural myocardial infarction.<sup>29</sup>

Periprocedural stroke is a rare, but serious, complication of PCI. The overall rate of periprocedural stroke in this study (0.5%) is comparable to that in previous reports.<sup>30</sup> PCI is an invasive procedure in which catheter manipulation mechanically stresses the arterial vascular system; this is likely the major cause for cerebral embolism during cardiac catheterization.<sup>31,32</sup> Patients with low and borderline ABIs might be in the progressive stage of atherosclerosis, and therefore they tend to experience periprocedural stroke more frequently than patients with normal ABIs.

### *One-year prognosis*

It is important to note that patients with a low ABI had a significantly higher incidence of NACE during the 1-year follow-up after hospital discharge. These patients suffered

hemorrhagic events, in particular. Patients with borderline ABIs also tended to experience CV death and major bleeding more frequently. In contrast, there was no significant difference in non-hemorrhage-related events between the 3 groups.

Compared with the normal ABI group, patients with low and borderline ABIs suffered more frequent hemorrhagic CV and stroke events. Patients with PAD are at higher risk for major hemorrhagic events than are patients with CAD.<sup>33</sup> Recently, Lee et al. reported that borderline ABI was associated with a higher stroke rate (including brain hemorrhage) in patients who underwent PCI than was normal ABI.<sup>34</sup> Although DES use did not vary significantly between groups, the rate of continuing dual antiplatelet therapy tended to be higher in the low and borderline ABI groups. Stenting of complex lesions, such as those involving the left main trunk, calcified lesions related to incomplete stent apposition, and diffuse lesions, may compel physicians to continue dual antiplatelet therapy.<sup>11</sup> These patients have significantly higher rates of atrial fibrillation and receive more anticoagulant therapy, both of which could lead to more frequent hemorrhagic events.<sup>35</sup> On the one hand, patients with low or borderline ABI were significantly older in this study; thus, it remains possible that more patients with atrial fibrillation who received anticoagulants were inadvertently categorized in the low or borderline ABI group in this study, and as a result, they suffered more hemorrhagic events. Nevertheless, in patients with PAD, the combination of oral anticoagulant and antiplatelet therapy has been associated with an increase in life-threatening bleeding.<sup>36</sup> Spontaneous bleeding after PCI was independently associated with higher long-term mortality and conveyed a risk comparable to that of myocardial infarction.<sup>37</sup> These findings suggest the importance of personalized antithrombotic therapy after PCI, based on each patient's risk of thrombotic and hemorrhagic events.

This study has limitations. The decision to perform PCI was at the operator's discretion; thus, selection bias could be present. There were significant differences in the rates of acute coronary syndrome across the groups, and 2% of patients who died owing to acute coronary syndrome before ABI measurement were excluded, which could have affected the in-hospital results. Accordingly, we established PCI-related complications instead of in-hospital mortality as the in-hospital endpoint. Moreover, we chose hospital discharge as a landmark point to reduce the influence of primary disease and PCI-related complications on 1-year prognosis.

## **Conclusions**

Patients with low and borderline ABIs had a significantly higher incidence of PCI-related complications and a less favorable 1-year prognosis than patients with normal ABIs, particularly in terms of major bleeding events; PCI operators should carefully monitor these patients. Routine ABI measurement before PCI may allow PCI operators to predict the risk of PCI-related complications and the 1-year prognosis after hospital discharge.

## **Acknowledgements**

We would like to thank all the investigators, clinical coordinators and institutions involved in the SHINANO registry.

Investigators: Hiroyuki Nakajima (Nagano Red Cross Hospital), Masanori Kobayashi (Matsumoto Kyoritsu Hospital), Hikaru Kimura, Eiichiro Mawatari (Saku Central Hospital), Hiroshi Akanuma (Iida Municipal Hospital), Toshio Sato, Takuya Maruyama (Shinonoi General Hospital), Shoji Hotta (Ina Central Hospital), Yuichi Kamiyoshi (Nagano Municipal Hospital), Noboru Watanabe (Hokushin General Hospital), Takayuki Eisawa, Kentaro

Hashidume et al. Prognostic Value of Ankle-Brachial Index

Shimada (Komoro Kosei Hospital), Shinichi Aso (Aizawa Hospital), Shinichiro Uchikawa (Azumino Red Cross Hospital), Noriyuki Sekimura (Okaya Municipal Hospital), Takehiro Morita (Nagano Matsushiro General Hospital).

Clinical coordinators: Minako Aono, Mebae Kobayashi.

#### Author contribution

All authors contributed to: (1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, and, (3) final approval of the version to be published.

**Disclosure Statement:** None of the authors have a real or perceived conflict of interest regarding the work in the manuscript.

**Funding:** This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.



**References**

1. Steg PG, Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherosclerosis. *JAMA*. 2007;297(11):1197-1206.
2. Diehm C, Allenberg JR, Pittrow D, et al. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. *Circulation*. 2009;120(21):2053-2061.
3. Carvounis CP, Nikas N. Prevalence of peripheral arterial disease in subjects at moderate cardiovascular risk: Greek results of the PANDORA study. *Hellenic J Cardiol*. 2014;55(4):294-304.
4. Criqui MH, Alberts MJ, Fowkes FG, et al. Atherosclerotic Peripheral Vascular Disease Symposium II: screening for atherosclerotic vascular diseases: should nationwide programs be instituted? *Circulation*. 2008;118(25):2830-2836.
5. Menke A, Muntner P, Wildman RP, Dreisbach AW, Raggi P. Relation of borderline peripheral arterial disease to cardiovascular disease risk. *Am J Cardiol*. 2006;98(9):1226-1230.
6. McDermott MM, Liu K, Criqui MH, et al. Ankle brachial index and subclinical cardiac and carotid disease. The Multi-Ethnic Study of Atherosclerosis. *Am J Epidemiol*. 2005;162(1):33-41.
7. Heald CL, Fowkes FG, Murray GD, Price JF; Ankle Brachial Index Collaboration. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. *Atherosclerosis*. 2006;189(1):61-69.
8. Bertrand OF, Bélisle P, Joyal D, et al. Comparison of transradial and femoral approaches for percutaneous coronary interventions: a systematic review and hierarchical Bayesian meta-analysis. *Am Heart J*. 2012;163(4):632-648.

9. Ikari Y, Matsukage T, Yoshimachi F, Masutani M, Saito S. Transradial and slender percutaneous coronary intervention: less invasive strategy in PCI. *Cardiovasc Interv Ther.* 2010;25(2):60-64.
10. Kirtane AJ, Gupta A, Iyengar S, et al. Safety and efficacy of drug-eluting and bare metal stents: comprehensive meta-analysis of randomized trials and observational studies. *Circulation.* 2009;119(25):3198-3206.
11. Montalescot G, Brieger D, Dalby AJ, Park SJ, Mehran R. Duration of dual antiplatelet therapy after coronary stenting: a review of the evidence. *J Am Coll Cardiol.* 2015;66(7):832-847.
12. Ness J, Aronow WS. Prevalence of coexistence of coronary artery disease, ischemic stroke, and peripheral arterial disease in older persons, mean age 80 years, in an academic hospital-based geriatrics practice. *J Am Geriatr Soc.* 1999;47(10):1255-1256.
13. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA.* 2006;295(2):180-189.
14. Saw J, Bhatt DL, Moliterno DJ, et al. The influence of peripheral arterial disease on outcomes: a pooled analysis of mortality in eight large randomized percutaneous coronary intervention trials. *J Am Coll Cardiol.* 2006;48(8):1567-1572.
15. Singh M, Lennon RJ, Darbar D, Gersh BJ, Holmes DR Jr, Rihal CS. Effect of peripheral arterial disease in patients undergoing percutaneous coronary intervention with intra coronary stents. *Mayo Clin Proc.* 2004;79(9):1113-1118.
16. Miura T, Miyashita Y, Motoki H, et al. In-hospital clinical outcomes of elderly patients ( $\geq$  80 years) undergoing percutaneous coronary intervention. *Circ J.* 2014;78(5):1097-1103.
17. Rooke TW, Hirsch AT, Misra S, et al. 2011 ACCF/AHA focused update of the guideline

- for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2011;124(18):2020-2045.
18. Greenland P, Abrams J, Aurigemma GP, et al. Prevention Conference V: Beyond secondary prevention: identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden: Writing Group III. *Circulation*. 2000;101(1):e16-e22.
19. Hoffman SJ, Routledge HC, Lennon RJ, et al. Procedural factors associated with percutaneous coronary intervention-related ischemic stroke. *JACC Cardiovasc Interv*. 2012;5(2):200-206.
20. Ankle Brachial Index Collaboration, Fowkes FG, Murray GD, et al. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA*. 2008;300(2):197-208.
21. Ogren M, Hedblad B, Isacson SO, Janzon L, Jungquist G, Lindell SE. Non-invasively detected carotid stenosis and ischaemic heart disease in men with leg arteriosclerosis. *Lancet*. 1993;342(8880):1138-1141.
22. Leng GC, Fowkes FG, Lee AJ, Dunbar J, Housley E, Ruckley CV. Use of ankle brachial pressure index to predict cardiovascular events and death: a cohort study. *BMJ*. 1996 ;313(7070):1440-1444.
23. Newman AB, Shemanski L, Manolio TA, et al. Ankle-arm index as a predictor of cardiovascular disease and mortality in the Cardiovascular Health Study. The Cardiovascular Health Study Group. *Arterioscler Thromb Vasc Biol*. 1999;19(3):538-545.
24. Sebastianski M, Narasimhan S, Graham MM, et al. Usefulness of the ankle-brachial index to predict high coronary SYNTAX scores, myocardium at risk, and incomplete coronary

- revascularization. *Am J Cardiol.* 2014 ;114(11):1745-1749.
25. Endo A, Kawamura A, Miyata H, et al. Angiographic lesion complexity score and in-hospital outcomes after percutaneous coronary intervention. *PLoS One.* 2015;10(6):e0127217.
26. Grossman PM, Gurm HS, McNamara R, et al. Percutaneous coronary intervention complications and guide catheter size: bigger is not better. *JACC Cardiovasc Interv.* 2009;2(7):636-644.
27. Hanna EB, Hennebry TA. Periprocedural myocardial infarction: review and classification. *Clin Cardiol.* 2010;33(8):476-483.
28. Mehran R, Dangas G, Mintz GS, et al. Atherosclerotic plaque burden and CK-MB enzyme elevation after coronary interventions: intravascular ultrasound study of 2256 patients. *Circulation.* 2000;101(6):604-610.
29. Herrmann J. Peri-procedural myocardial injury: 2005 update. *Eur Heart J.* 2005;26(23):2493-2519.
30. Werner N, Bauer T, Hochadel M, et al. Incidence and clinical impact of stroke complicating percutaneous coronary intervention: results of the Euro heart survey percutaneous coronary interventions registry. *Circ Cardiovasc Interv.* 2013;6(4):362-369.
31. Keeley EC, Grines CL. Scraping of aortic debris by coronary guiding catheters: a prospective evaluation of 1,000 cases. *J Am Coll Cardiol.* 1998;32(7):1861-1865.
32. Hamon M, Gomes S, Oppenheim C, et al. Cerebral microembolism during cardiac catheterization and risk of acute brain injury: a prospective diffusion-weighted magnetic resonance imaging study. *Stroke.* 2006;37(8):2035-2038.
33. Achterberg S, Visseren FL, Kappelle LJ, et al. Differential propensity for major hemorrhagic events in patients with different types of arterial disease. *J Thromb Haemost.*

2011;9(9):1724-1729.

34. Lee SH, Choi SH, Kim EK, et al. Borderline ankle-brachial index is associated with poor short-term clinical outcome after coronary artery intervention. *Atherosclerosis*. 2016;249:186-190.
35. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381(9872):1107-1115.
36. Warfarin Antiplatelet Vascular Evaluation Trial Investigators, Anand S, Yusuf S, et al. Oral anticoagulant and antiplatelet therapy and peripheral arterial disease. *N Engl J Med*. 2007;357(3):217-227.
37. Kazi DS, Leong TK, Chang TI, Solomon MD, Hlatky MA, Go AS. Association of spontaneous bleeding and myocardial infarction with long-term mortality after percutaneous coronary intervention. *J Am Coll Cardiol*. 2015;65(14):1411-1120.

**Figure Legends**

Figure 1. Patient flow chart

PCI, percutaneous coronary intervention; ABI, ankle-brachial index

Figure 2. Percutaneous coronary intervention-related complications

PCI, percutaneous coronary intervention; ABI, ankle-brachial index; MI, myocardial infarction; CIN, contrast-induced nephropathy; CCE, cholesterol crystal embolization. \* $p < 0.05$  vs normal ABI

Figure 3. Kaplan-Meier analysis for net adverse clinical events

ABI, ankle-brachial index. \*log rank  $p < 0.05$  vs normal ABI

Figure 4. One-year clinical outcome incidence. (A) Proportion of hemorrhage-related deaths among all cardiovascular deaths. (B) Proportion of intracranial bleeding among all strokes.

ABI, ankle-brachial index. \* $p < 0.05$  vs normal ABI

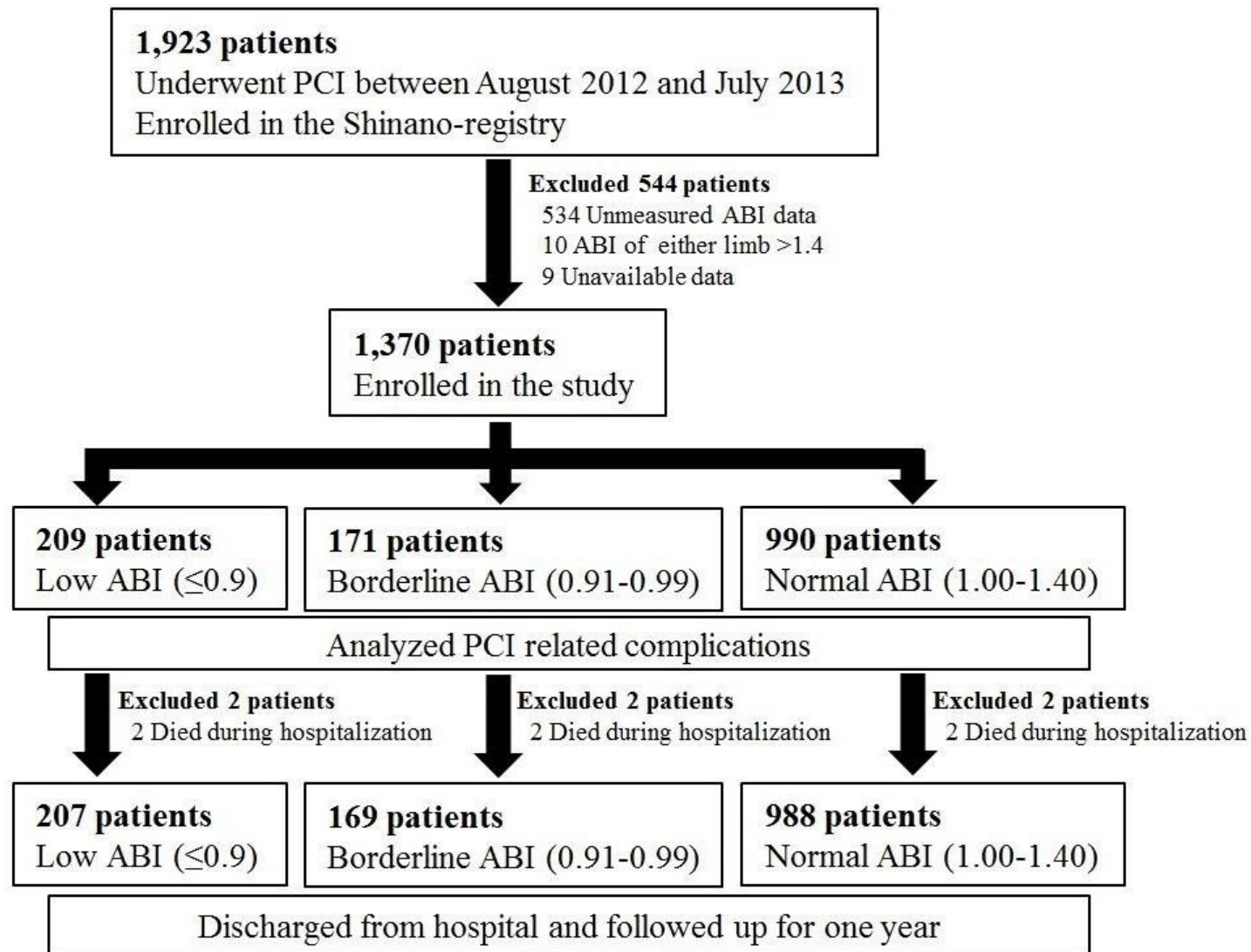


Figure 1

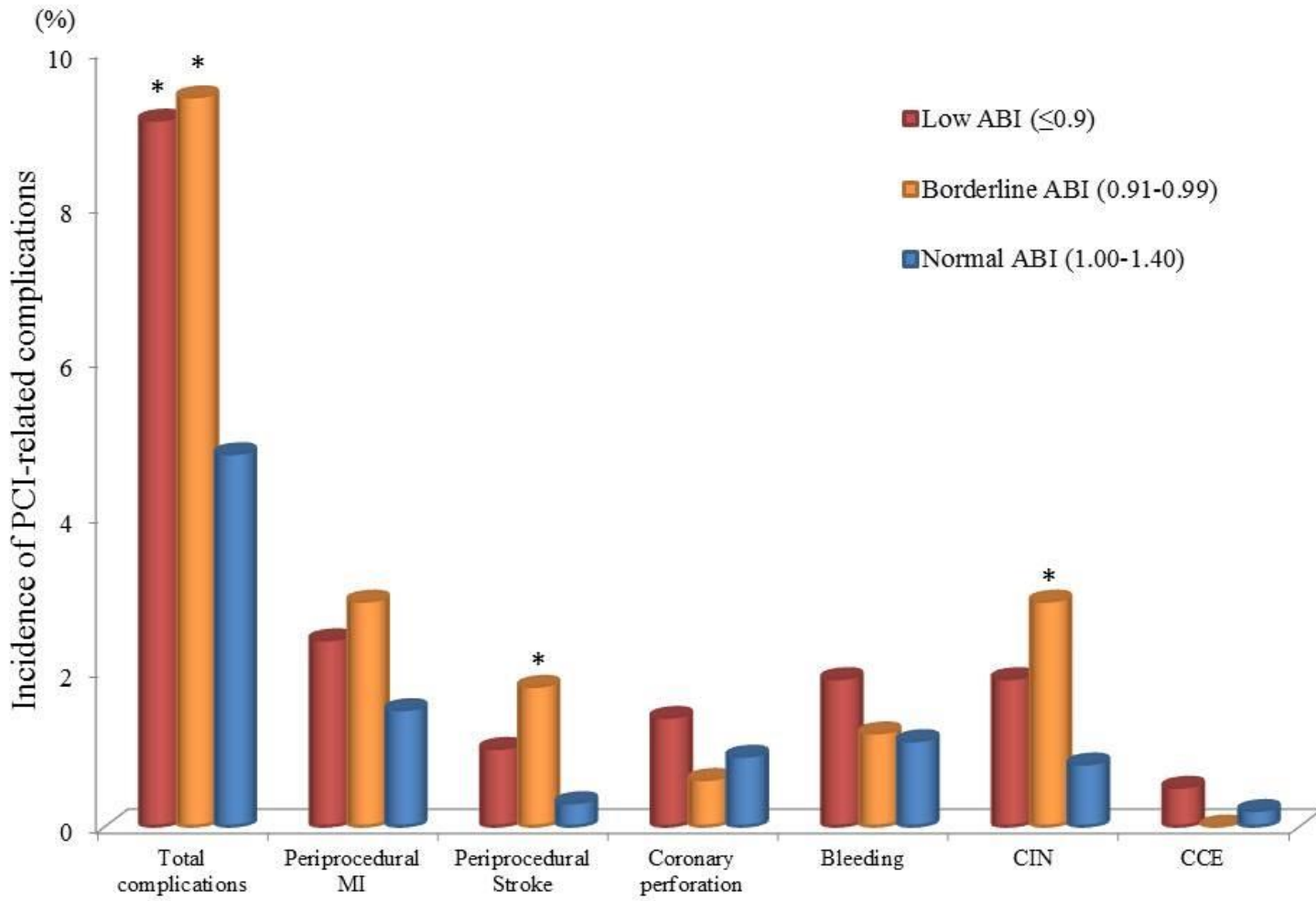
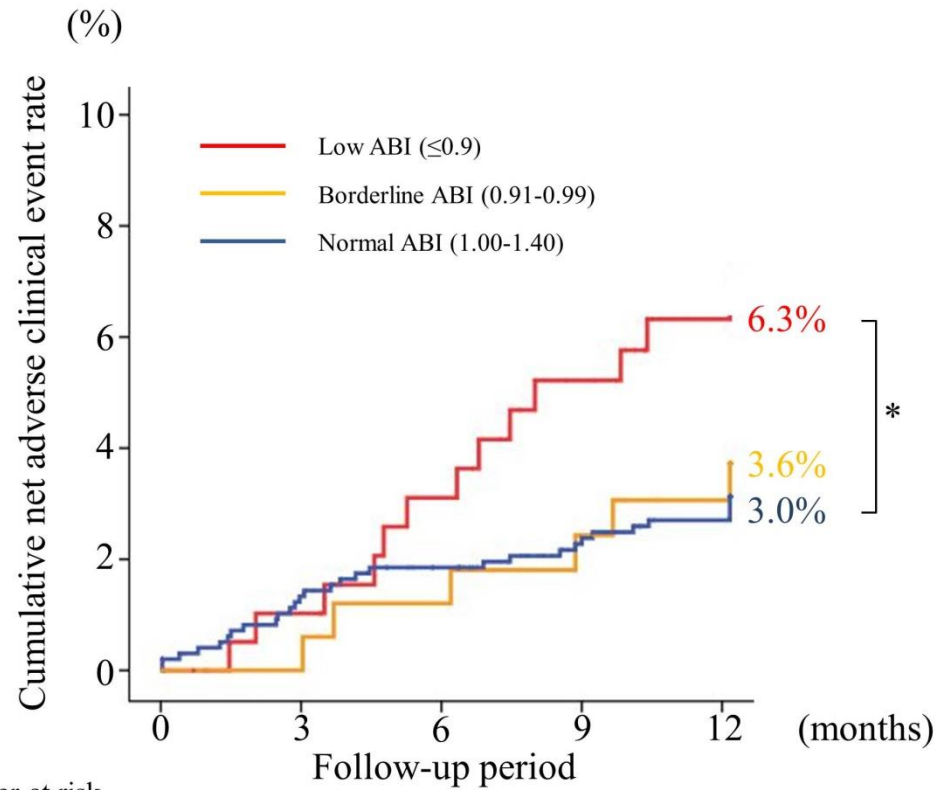


Figure 2





Number at risk		0	3	6	9	12
Low ABI		206	193	185	176	165
Borderline ABI		168	166	164	156	147
Normal ABI		987	958	941	915	897

**Figure 3**

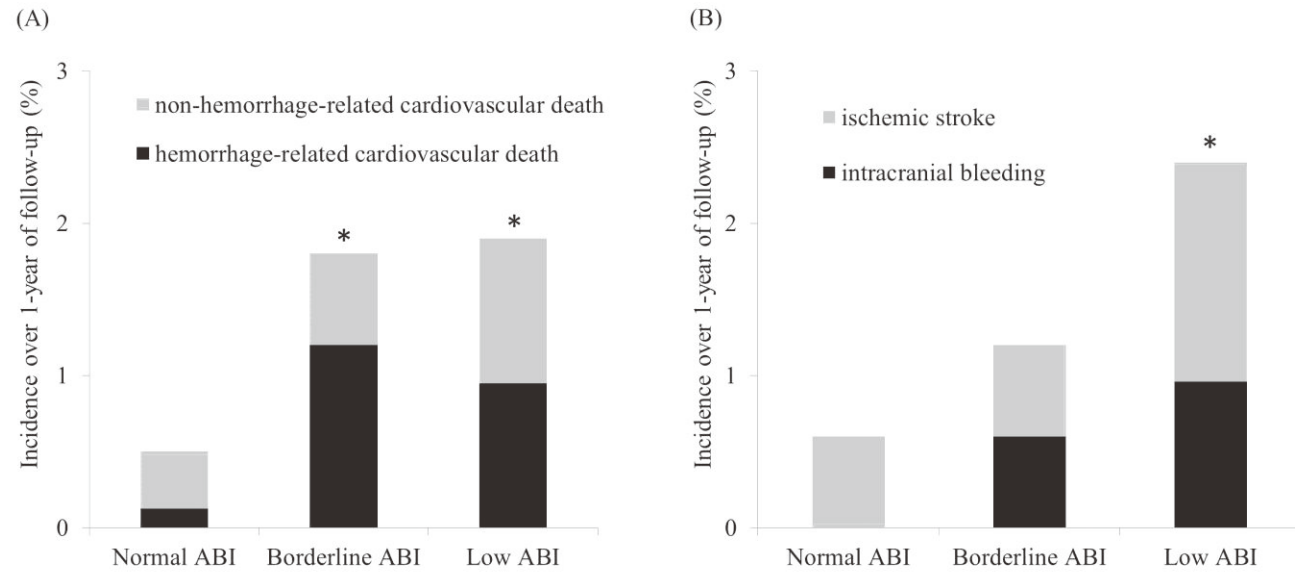


Figure 4

**Table 1.** Baseline and laboratory characteristics of the study population based on ankle-brachial index**Table 1.** Baseline and laboratory characteristics of the study population based on ankle-brachial index

Variables	ABI group			p-value
	Low ( $\leq 0.90$ ) <i>n</i> = 209	Borderline (0.91-0.99) <i>n</i> = 171	Normal (1.00-1.40) <i>n</i> = 990	
Age, years	76.5 (8.6)	72.1 (11.7)	68.8 (10.8)	<0.001
Female sex, %	27.8	30.4	18.9	<0.001
BMI, kg/m <sup>2</sup>	22.6 (3.8)	23.6 (3.9)	24.1 (3.6)	<0.001
Current smoker, %	18.7	18.3	20.1	0.799
Previous smoker, %	53.4	49.4	55.0	0.403
Hypertension, %	80.4	75.4	72.4	0.053
Dyslipidemia, %	60.8	60.8	61.5	0.973
Diabetes, %	53.6	34.7	32.8	<0.001
Hemodialysis, %	14.4	5.8	3.5	<0.001
Atrial fibrillation, %	13.9	19.9	8.6	<0.001
Total cholesterol, mg/dL	171 (41)	184 (45)	183 (42)	<0.001
HDL cholesterol, mg/dL	45 (12)	47 (14)	48 (13)	0.008
LDL cholesterol, mg/dL	102 (35)	113 (39)	110 (35)	0.006
Triglycerides, mg/dL	126 (88)	133 (74)	139 (88)	0.031
HbA <sub>1c</sub> , %	6.5 (1.2)	6.2 (1.1)	6.2 (1.2)	<0.001
Serum creatinine, mg/dL	1.85 (2.38)	1.29 (1.45)	1.12 (1.35)	<0.001
eGFR, mL/min/1.73 m <sup>2</sup>	51.8 (25.9)	59.3 (26.3)	64.6 (22.0)	<0.001
ABI	0.73 (0.14)	0.96 (0.03)	1.12 (0.07)	<0.001

**Table 1.** Baseline and laboratory characteristics of the study population based on ankle-brachial index**Medication at discharge**

Aspirin, %	96.6	98.8	98.2	0.222
Thienopyridines, %	89.4	91.2	91.7	0.581
Anticoagulant, %	16.7	18.1	11.1	0.008
ACEI / ARB, %	68.9	72.4	69.9	0.754
Beta-blockers, %	44.2	43.5	43.4	0.987
Statins, %	65.0	70.0	75.1	0.008
EPA, %	3.9	4.7	3.6	0.765
Insulin, %	15.9	10.3	6.5	<0.001

**Medication at 1-year after hospital discharge**

Continuing DAPT	57.8	59.1	51.8	0.106
Anticoagulant, %	17.2	17.5	12.1	0.036

---

ABI, ankle brachial index; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; eGFR, estimated glomerular filtration rate; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; EPA, eicosapentaenoic acid; DAPT, dual antiplatelet therapy.

Values are presented as mean (standard deviation) or percentage.

**Table 2.** Lesion characteristics of the study population based on ankle-brachial index**Table 2.** Lesion characteristics of the study population based on ankle-brachial index.

Variables	ABI group			p
	Low	Borderline	Normal	
	( $\leq 0.90$ )	(0.91-0.99)	(1.00-1.40)	
	<i>n</i> = 209	<i>n</i> = 171	<i>n</i> = 990	
<b>Lesion profile</b>				
De novo lesions, %	87.6	88.9	90.0	0.565
ACS, %	33.5	43.3	44.0	0.019
Multivessel disease, %	47.5	48.3	34.8	<0.001
Diffuse lesions, %	28.5	23.4	19.7	0.021
LMT lesions, %	3.8	5.2	1.0	<0.001
Ostial lesions, %	12.0	7.6	6.4	0.020
Calcified lesions, %	40.7	28.8	27.3	0.001
Bifurcation lesions, %	25.8	22.8	24.6	0.791
CTO lesions, %	6.3	5.8	6.1	0.985
SYNTAX score	14.1 (10.0)	13.9 (9.4)	11.8 (8.1)	0.001
<b>PCI procedure</b>				
TFI, %	34.0	39.8	28.6	0.033
TBI, %	10.0	2.9	2.6	<0.001
TRI, %	56.0	57.3	68.8	0.001

**Table 2.** Lesion characteristics of the study population based on ankle-brachial index

DES use, %	53.1	51.8	47.4	0.234
BMS use, %	29.7	36.3	38.4	0.059
Rotational atherectomy, %	5.3	2.3	1.6	0.005
Single stent KBT, %	4.8	4.7	3.8	0.710
IABP use, %	4.8	7.0	3.7	0.139

---

ABI, ankle-brachial index; ACS, acute coronary syndrome; LMT, left main trunk; CTO, chronic total occlusion; PCI, percutaneous coronary intervention; TFI, trans-femoral intervention; TBI, trans-brachial intervention; TRI, trans-radial intervention; DES, drug-eluting stent; BMS, bare-metal stent; KBT, kissing balloon technique; IABP, intra-aortic balloon pumping.

Values are presented as mean (standard deviation) or percentage.

**Table 3.** Relationships between ankle brachial index and the development of adverse events during the 1-year follow-up period after hospital discharge

**Table 3.** Relationships between ankle brachial index and the development of adverse events during the 1-year follow-up period after hospital discharge.

ABI group	Number of events	Incidence (%)		Unadjusted		Multivariable adjusted <sup>a</sup>		
		HR	95%CI	HR	95%CI	HR	95%CI	p
<b>Net adverse clinical events (composite of cardiovascular death, myocardial infarction, stroke, major bleeding)</b>								
Normal (1.00-1.40)	30	3.0	1.00 (reference)	1.00	(reference)	1.00	(reference)	
Borderline (0.91-0.99)	6	3.6	1.14 0.47-2.72	1.10	0.45-2.68	1.10	0.45-2.68	0.838
Low ( $\leq$ 0.90)	13	6.3	2.21 1.15-4.23	2.27	1.12-4.61	2.27	1.12-4.61	0.023
<b>Cardiovascular death</b>								
Normal (1.00-1.40)	5	0.5	1.00 (reference)	1.00	(reference)	1.00	(reference)	
Borderline (0.91-0.99)	3	1.8	3.51 0.84-14.67	3.51	0.82-15.08	3.51	0.82-15.08	0.091
Low ( $\leq$ 0.90)	4	1.9	3.94 1.06-14.68	4.94	1.19-20.58	4.94	1.19-20.58	0.028
<b>Myocardial infarction</b>								
Normal (1.00-1.40)	10	1.0	1.00 (reference)	1.00	(reference)	1.00	(reference)	

**Table 3.** Relationships between ankle brachial index and the development of adverse events during the 1-year follow-up period after hospital discharge

Borderline (0.91-0.99)	0								
Low ( $\leq 0.90$ )	1	0.5 <sup>b</sup>	0.27	0.04-2.12	0.214 <sup>b</sup>	0.25	0.03-2.01	0.192 <sup>b</sup>	
<b>Stroke</b>									
Normal (1.00-1.40)	6	0.6	1.00	(reference)		1.00	(reference)		
Borderline (0.91-0.99)	2	1.2	1.97	0.40-9.78	0.405	2.07	0.41-10.49	0.378	
Low ( $\leq 0.90$ )	5	2.4	4.95	1.43-17.11	0.011	4.42	1.14-17.15	0.032	
<b>Major bleeding</b>									
Normal (1.00-1.40)	9	0.9	1.00	(reference)		1.00	(reference)		
Borderline (0.91-0.99)	5	3.0	2.93	1.00-8.58	0.050	3.21	1.05-9.79	0.041	
Low ( $\leq 0.90$ )	7	3.4	3.86	1.44-10.35	0.007	3.89	1.28-11.82	0.017	

ABI, ankle-brachial index; HR, hazard ratio; CI, confidence interval.

<sup>a</sup>Adjusted for age (quartiles), sex, current smoking, hypertension, dyslipidemia and diabetes.

<sup>b</sup>Borderline and low ABI groups were combined.