Association of borderline ankle-brachial index with mortality and the incidence of peripheral artery disease in diabetic patients

夏秋，千晴

Association of borderline ankle-brachial index with mortality and the incidence of peripheral artery disease in diabetic patients

Chiharu Natsuaki [a], Toyoshi Inoguchi [a,b,*], Yasutaka Maeda [a], Tomomi Yamada [c], Shuji Sasaki [a], Noriyuki Sonoda [a,b], Michio Shimabukuro [d], Hajime Nawata [e], Ryoichi Takayanagi [a]

[a] Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
[b] Innovation Center for Medical Redox Navigation, Kyushu University, Fukuoka, Japan
[c] Department of Clinical Epidemiology and Biostatistics, Graduate School of Medicine, Osaka University, Osaka, Japan
[d] Institute of Health Biosciences, The University of Tokushima Graduate School, Tokushima, Japan
[e] Seiwakai, Muta Hospital, Fukuoka, Japan

ABSTRACT

Objective: Peripheral artery disease (PAD) and diabetes mellitus are significant risk factors for all-cause death or cardiovascular death. PAD occurs more frequently in diabetic than in non-diabetic patients. However, the association of ankle-brachial index (ABI), especially borderline ABI, with clinical outcomes has not been fully elucidated in diabetic patients. This study aimed to investigate the association of ABI with mortality and the incidence of PAD in Japanese diabetic patients.
Methods: This observational study included 3981 diabetic patients (61.0 ± 11.8 years of age, 59.4% men), registered in the Kyushu Prevention Study for Atherosclerosis. Patients were divided into 3 groups according to the value of ABI at baseline: ABI ≤ 0.90 (abnormal ABI:354 patients), $0.91 \leq$ ABI ≤ 0.99 (borderline ABI:333 patients), and $1.00 \leq$ ABI ≤ 1.40 (normal ABI:3294 patients).
Results: Cumulative incidence of all-cause death was significantly higher in patients with abnormal and borderline ABI than in those with normal ABI (34.4% vs. 13.5%, $P < 0.0001$ and 26.1% vs. 13.5%, $P < 0.0001$, respectively). In multivariate analysis, the risks for all-cause death in patients with abnormal ABI (HR:2.16; 95%CI:1.46–3.14; $P = 0.0002$) and borderline ABI (HR:1.78; 95%CI:1.14–2.70; $P = 0.01$) were significantly higher than in those with normal ABI. The incidence of PAD was remarkably higher in patients with borderline ABI than in those with normal ABI (32.2% vs.9.6%, $P < 0.0001$). After adjustment, the risk for PAD was significantly higher in patients with borderline ABI than in those with normal ABI (HR:3.10; 95%CI:1.90–4.95; $P < 0.0001$).
Conclusions: Borderline ABI in diabetic patients was associated with significantly higher risks for mortality and PAD compared with normal ABI.

© 2014 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Peripheral arterial disease (PAD) has been widely accepted as a significant risk factor for all-cause death or cardiovascular death [1–9]. Diabetes is also regarded as a significant risk factor for death [10,11], and PAD is more frequent in diabetic patients than in non-diabetic patients [12–15]. Ankle-brachial index (ABI) is used to diagnose PAD with simplicity, inexpensiveness, and high specificity [16]. The American College of Cardiology and the American Heart Association (ACC/AHA) guidelines have recommended ABI ≤ 0.90 as the diagnostic criterion for PAD [17]. The diagnostic criteria for PAD with diabetes mellitus defined by the American Diabetes Association based on ABI are as follows: <0.40 (severe obstruction), 0.40–0.69 (moderate obstruction), 0.70–0.90 (mild), 0.91–1.30 (normal), and >1.30 (poorly compressible). Accordingly, most studies investigating the association of ABI and mortality have focused on ABI ≤ 0.90 as an indicator of PAD. However, ABI sometimes presents with erroneously high values because of poor compression caused by diffused atherosclerosis in diabetic patients [18]. The 2011 ACC/AHA guidelines for the management of patients

* Corresponding author. Innovation Center for Medical Redox Navigation, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Tel.: +81 92 642 5284; fax: +81 92 642 5287.
E-mail address: toyoshi.inoguchi@gmail.com (T. Inoguchi).

with PAD have recommended $0.91 \leq ABI \leq 0.99$ as the category of borderline ABI [17], and patients with not only abnormal ABI ($ABI \leq 0.90$) but also borderline ABI ($0.91 \leq ABI \leq 0.99$) could be the high risk population in diabetic patients. However, few studies have assessed the relationship of all values of ABI, i.e., is limited to ≤ 0.90, with all-cause death, cardiovascular death and the incidence of PAD in diabetic patients.

Thus, actual condition of all-cause death and cardiovascular death in diabetic patients with $ABI \leq 0.99$, especially those with borderline ABI ($0.91 \leq ABI \leq 0.99$), should be investigated. Furthermore, the incidence of PAD in diabetic patients with borderline ABI and normal ABI should also be revealed. Therefore, this study investigated the association of ABI with all-cause mortality, cardiovascular mortality, and the incidence of PAD in diabetic patients in a large-scale Japanese population.

2. Methods

2.1. Subjects

This observational study was based on data from the Kyushu Prevention Study for Atherosclerosis, a prospective multi-center survey. Consecutive outpatients with diabetes ($N = 4327$) who regularly visited the Kyushu University Hospital and its 17 related hospitals, and the University of the Ryukyus, and its six related hospitals, were enrolled from 2001 to 2003 for the survey. The participants provided informed consent. Measurement of height, weight, systolic and diastolic blood pressure, neurologic and eye fundus examinations, and laboratory blood and urine tests were performed at baseline. Medical records included the use of other medications (including angiotensin II receptor blocker (ARB) and/or angiotensin-converting enzyme inhibitor (ACEI), statins, anti-platelet agent (APA), and/or anti-thrombotic agent (ATA)). This study was approved by the relevant review boards or ethics committees of the participating institutions.

2.2. Clinical assessment (medical history and definition at baseline)

At baseline, systolic blood pressure in the arms and legs of each subject was measured, and ABI was automatically calculated, by a non-invasive vascular screening device (Vascular Profiling System-2000, Omron Colin Co., Ltd., Komaki, Japan), as the ratio of systolic blood pressure in the leg to that in the arm on each side. Valid information was acquired from 3984 diabetic patients during the baseline period. The lower of the ABI values from both sides was used [19]. ABI was categorized into three ranges according to the ACC/AHA guidelines: $ABI \leq 0.90$ (abnormal ABI), $0.91 \leq ABI \leq 0.99$ (borderline ABI), and $1.00 \leq ABI \leq 1.40$ (normal ABI). The current analysis included 3981 patients after excluding 3 patients with $ABI > 1.4$ [17].

Diabetes was considered to be present if the fasting plasma glucose level was ≥ 126 mg/dl, the glucose level was >200 mg/dl at 2 h after a 75-g oral glucose tolerance test, the casual plasma glucose level was >200 mg/dl, or the patient was taking oral antihyperglycemic agents and/or using insulin. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or there was current use of any antihypertensive medication. Dyslipidemia was determined by a previous diagnosis, or total cholesterol was ≥ 220 mg/dl and/or triglyceride was ≥ 150 mg/dl and/or high-density lipoprotein cholesterol was <40 mg/dl. Smoking habit was defined as current smoking as obtained by interview. Diabetic neuropathy was diagnosed by diabetologists from typical symptoms and combinations of more than one test of examining pinprick, temperature, and vibration perception (using a 128-Hz tuning fork), 10-g monofilament

pressure sensation at the distal halluces, and ankle reflexes. Retinopathy was assessed with a fundus examination by independent ophthalmologists. Nephropathy was defined with the persistent albuminuria in the range of ≥ 300 mg/g by measurement of the albumin-to-creatinine ratio in random urine spot collections, which were measured at least two times: at baseline and before and/or after registration.

Primary endpoint in the present analysis was all-cause death. Secondary endpoint included cardiovascular death and the incidence of PAD.

Death was regarded as cardiovascular in origin unless obvious non cardiovascular causes could be identified [20]. Vascular death was defined as death related to aortic, cerebral, renal, and other vascular diseases in origin. PAD was defined with the last $ABI \leq 0.90$ during follow-up.

Median follow-up duration was 3.0 years (inter-quartile range 1.0–5.1).

2.3. Data collection and follow-up

Follow-up data were obtained from hospital charts, by direct contact with patients or from referring physicians. ABI was measured every year during visits to the relative institutions. Follow-up intervals were calculated from the day of ABI measurement. Enrollment duration was 1081 (inter-quartile range: 365–1842) days.

2.4. Statistical analysis

Continuous variables are presented as means $\pm$ SD and discrete variables are expressed as numbers and percentages. Variables in each group were compared with analysis of variance. The cumulative occurrences were assessed by the Kaplan–Meier method, and differences were estimated with the Log-rank test.

The adjusted risk was determined using the Cox proportional hazard model by incorporating the ABI categories together with the 13 risk-adjusting variables selected from clinically relevant factors shown in Table 1. Age, one of 13 variables in the risk-adjustment, was divided by10 to estimate the risk for each 10-year increase. In the Cox proportional hazard model, regarding all-cause death and cardiovascular death, we developed dummy codes for abnormal ABI and borderline ABI, with normal ABI as the reference. The effect of each ABI level category compared with the reference category was expressed as the hazard ratio (HR) and 95% confidence interval (CI).

Statistical analysis was performed with JMP Version 9.0 (SAS institute Inc, Cary, NC) software. All the statistical analyses were two-tailed and P values of <0.05 were considered statistically significant.

3. Results

3.1. Characteristics of subjects at baseline

Table 1 displays the demographic and clinical characteristics of the participants.

Among 3981 patients, 3294 patients (82.7%) had normal ABI, 333 patients (8.4%) had borderline ABI, and 354 patients (8.9%) had abnormal ABI. There were no significant differences in dyslipidemia, smoking, BMI, and HbA$_{1c}$ amongst the three groups. There were significant differences in age, gender, hypertension, diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy. Except gender, all increased with decreasing ABI. Regarding the medications, the prescription rates were significant different across the 3 groups (Table 1).

Table 1
Baseline characteristics.

Variables	ABI ≤ 0.90	0.91 ≤ ABI ≤ 0.99	1.00 ≤ ABI ≤ 1.40	P Value
	(N = 354)	(N = 333)	(N = 3294)	
Clinical characteristics				
Age (years)	67.8 ± 11.5	62.0 ± 13.6	60.2 ± 11.3	<0.0001
Male	196 (55.3%)	180 (54.1%)	1989 (60.4%)	0.02
Hypertension	285 (80.1%)	214 (64.3%)	1981 (60.1%)	<0.0001
Dyslipidemia	188 (57.0%)	174 (55.8%)	1773 (57.7%)	0.78
Diabetic retinopathy	130 (36.7%)	106 (31.8%)	786 (23.9%)	<0.0001
Diabetic neuropathy	151 (42.7%)	92 (27.6%)	723 (21.9%)	<0.0001
Diabetic nephropathy	151 (42.7%)	99 (29.7%)	705 (21.4%)	<0.0001
Smoking	75 (21.2%)	81 (24.3%)	811 (24.6%)	0.35
BMI (kg/m^2)	24.1 ± 4.32	24.6 ± 4.37	24.6 ± 4.05	0.05
HbA$_{1c}$ (%)	7.86 ± 1.81	8.01 ± 2.09	7.74 ± 2.16	0.07
Baseline medication				
Statins	99 (28.0%)	95 (28.5%)	629 (19.1%)	<0.0001
ARB and/or ACEI	138 (39.0%)	91 (27.3%)	754 (22.9%)	<0.0001
APA and/or ATA	147 (41.5%)	71 (21.3%)	449 (13.6%)	<0.0001

Data are means ± standard deviation or number (percentage). ABI was measured at baseline. ABI indicates ankle-brachial index; BMI, body mass index; HbA$_{1c}$, glycosylated hemoglobin; ARB, angiotensin II receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; APA, anti-platelet agent; ATA, anti-thrombotic agent.

3.2. Change of ABI value during follow-up

Through the follow-up, 74.8% (119/159) of patients with ABI ≤ 0.90, 73.8% (124/168) of patients with 0.91 ≤ ABI ≤ 0.99 and 49.3% (791/1605) of patients with 1.00 ≤ ABI ≤ 1.40 had no change or increase of ABI (Supplemental Figure).
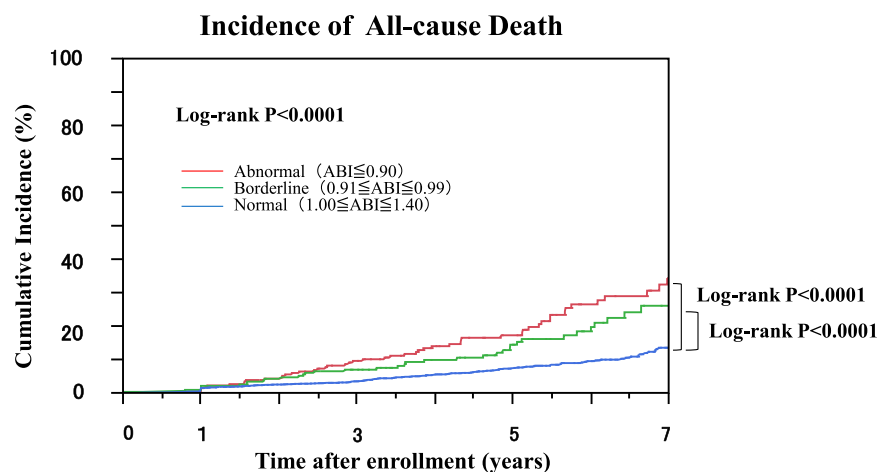
3.3. All-cause death and cardiovascular death

The cumulative occurrence of both all-cause death and cardiovascular death during follow-up were significantly higher in subjects with abnormal and borderline ABI than in those with normal ABI (Fig. 1, Fig. 2). Patients with borderline ABI (all-cause death; HR: 1.78; 95% CI: 1.14–2.70; P = 0.01, cardiovascular death; HR: 2.68;

95% CI: 1.51–4.56; P = 0.0012) and abnormal ABI (all-cause death; HR: 2.16; 95% CI: 1.46–3.14; P = 0.0002, cardiovascular death; HR: 2.00; 95% CI: 1.15–3.37; P = 0.02) had significantly higher risk for both all-cause death and cardiovascular death compared to those with normal ABI, after adjustment (Table 2, Supplemental Table 1).

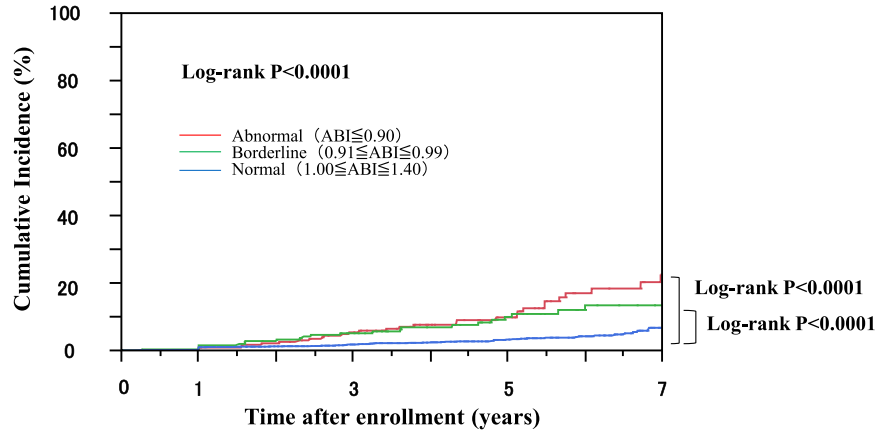### 3.4. Incidence of peripheral artery disease

Regarding the incidence of PAD, cumulative incidence was remarkably higher in patients with borderline ABI than in those with normal ABI (Fig. 3). After adjustment, patients with borderline ABI had significantly higher risk for PAD compared to those with normal ABI (HR: 3.10; 95% CI: 1.90–4.95; P < 0.0001) (Supplemental Table 2).

Incidence of All-cause Death

Log-rank P<0.0001

Abnormal (ABI≦0.90)
Borderline (0.91≦ABI≦0.99)
Normal (1.00≦ABI≦1.40)

Log-rank P<0.0001
Log-rank P<0.0001

Interval	0 day	1year	3years	5years	7years
Abnormal					
N of patients at risk	354	352	188	106	35
N of events		2	24	37	52
Cumulative incidence		1.4%	9.6%	17.2%	34.4%
Borderline					
N of patients at risk	333	330	186	105	31
N of events		3	18	28	37
Cumulative incidence		2.1%	6.9%	14.4%	26.1%
Normal					
N of patients at risk	3294	3278	1589	805	183
N of events		16	89	137	163
Cumulative incidence		1.5%	3.5%	7.5%	13.5%

Fig. 1. Cumulative incidence of all-cause death according to the ankle-brachial index (ABI) category.

Fig. 2. Cumulative incidence of cardiovascular death according to the ankle-brachial index (ABI) category.

4. Discussion

The main findings of the current analysis are that in comparison with diabetic patients with normal ABI: (1) diabetic patients with abnormal ABI had the higher occurrences of all-cause death and cardiovascular death, and abnormal ABI was a significant risk factor for all-cause and cardiovascular mortality even after adjustment; and (2) diabetic patients with borderline ABI had the significantly higher occurrences of all-cause death and cardiovascular death, and

borderline ABI was a significant risk factor for all-cause and cardiovascular mortality even after adjustment; and (3) diabetic patients with borderline ABI had a significantly higher incidence of PAD, and borderline ABI was a significant risk factor for PAD even after adjustment.

In this large scale study, abnormal ABI was associated with significantly higher risk for all-cause death and cardiovascular death. A previous meta-analysis in a general population reported that ABI ≤ 0.90 had a significantly increased risk of all-cause death. Concerning cardiovascular death, as the value of ABI gets lower, ABI ≤ 0.90 had increased risk compared with the reference of 1.11 ≤ ABI ≤ 1.20 [7].

In this study, borderline ABI was also associated with significantly higher risk for all-cause death and cardiovascular death. One meta-analysis in unselected subjects displayed that all-cause death and cardiovascular death followed a U-shaped curve across the spectrum of ABI values, and there was a significantly increased risk in patients with borderline ABI (all-cause death; men; HR: 1.61; 95% CI: 1.47–1.77, women; HR: 1.52; 95% CI: 1.38–1.67, cardiovascular death; HR: 1.68; 95% CI: 1.40–2.00, women; HR: 1.84; 95% CI: 1.53–2.22) [7]. When we compare the results of this report with ours, the risk for all-cause and cardiovascular mortality in patients with borderline ABI seems to be more pronounced in those with diabetes, despite our wider reference of 1.00 ≤ ABI ≤ 1.40. As most previous studies evaluating the cumulative occurrences of all-cause death and cardiovascular death in borderline ABI have been performed in unselected subjects, our study in a diabetic population is worthy of note.

Hyperglycemia and insulin resistance play a role in the loss of normal nitric oxide homeostasis, which causes vascular smooth muscle cell migration and proliferation, after that atherosclerosis associating with precipitation of clinical events is accelerated [21]. Thus, most diabetic patients demonstrate endothelial dysfunction and vascular irregularities [22]. However, in patients with borderline ABI, these changes are considered to be more remarkable than

Table 2
Univariate and multivariate analysis for all-cause death.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	P Value	H.R.	95% CI	P Value
Borderline ABI (0.91 ≤ ABI ≤ 0.99)[a]	1.95	1.36–2.70	0.0004	1.78	1.14–2.70	0.01
Abnormal ABI (ABI ≤ 0.90)[a]	2.69	1.95–3.62	<0.0001	2.16	1.46–3.14	0.0002
Age (for each 10-year increase)	1.45	1.29–1.63	<0.0001	1.27	1.09–1.49	0.002
Male	1.26	0.98–1.63	0.07	1.38	1.01–1.90	0.04
Hypertension	1.70	1.30–2.25	<0.0001	1.32	0.92–1.91	0.14
Dyslipidemia	1.09	0.84–1.42	0.54	1.27	0.94–1.72	0.12
Diabetic retinopathy	1.11	0.85–1.44	0.44	0.89	0.64–1.22	0.47
Diabetic neuropathy	1.21	0.93–1.57	0.16	0.92	0.66–1.27	0.61
Diabetic nephropathy	1.74	1.35–2.23	<0.0001	1.57	1.13–2.16	0.007
Smoking	0.73	0.53–0.98	0.04	0.87	0.60–1.24	0.44
BMI (for each 1 kg/m² increase)	0.98	0.95–1.01	0.26	0.99	0.95–1.03	0.62
HbA$_{1c}$ (for each 1% increase)	1.04	0.97–1.10	0.27	1.06	0.98–1.13	0.15
Statins	0.94	0.70–1.25	0.70	0.84	0.58–1.18	0.33
ARB and/or ACEI	1.31	1.00–1.69	0.05	0.89	0.62–1.25	0.49
APA and/or ATA	2.00	1.54–2.59	<0.0001	1.46	1.03–2.04	0.03

ABI was measured at baseline. HR indicates hazard ratio; CI, confidence interval. Other abbreviations are as in Table 1.
[a] Patients with 1.00 ≤ ABI ≤ 1.40 were used as the reference.

Incidence of Peripheral Artery Disease
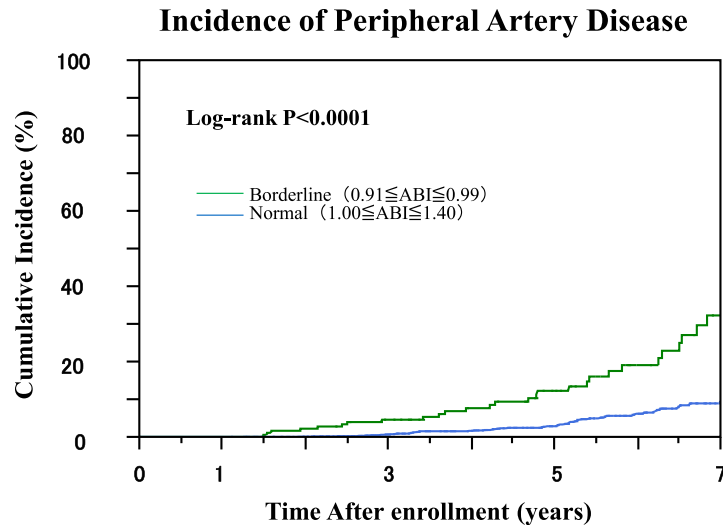
Interval	0 day	1year	3years	5years	7years
Borderline					
N of patients at risk	333	188	152	83	25
N of events		0	8	17	28
Cumulative incidence		0%	4.6%	12.2%	32.2%
Normal					
N of patients at risk	3294	1676	1277	632	136
N of events		0	9	30	55
Cumulative incidence		0%	0.6%	2.8%	9.6%

Fig. 3. Cumulative incidence of peripheral artery disease according to the ankle-brachial index (ABI) category.

in those with normal ABI. It was reported that an ABI of 0.90—0.99 was associated with a significantly higher prevalence of subclinical atherosclerosis in comparison with an ABI of 1.10—1.29 [2], and the endothelial dysfunction, assessed by the reactive hyperemia index, was detected in 15/66 (23%) of subjects with ABI values between 0.90 and 1.00 [23]. The endothelium is the target of vascular inflammation and thrombosis, which induces the atherosclerosis disease. In addition, inflammation maintained because of the impairment of wound healing in diabetes predispose to cardio-vascular complications [24]. These adverse reactions might be one of the causes for higher mortality in patients with borderline ABI.

The impairment of the elastic and muscular arteries in diabetes [25], resulting in poorly compressible vessels, which can increase the apparent ABI values [17]. There is a report that diabetic patients with ABI>0.90 had low blood flow in the lower-leg arteries [26], which suggested that measured ABI values might not reflect the actual condition of the peripheral arteries, particularly in diabetes. We might miss the patients with PAD if we adopt the current cut-off value of ABI ≤ 0.90 in diabetic patients. We should also deal with borderline ABI carefully, especially in diabetic patients.

This study also revealed a positive association between the incidence of PAD and the severity of ABI in diabetes, and indicated that borderline ABI is a predictor not only for mortality but also for prognosis of cardiovascular dysfunction in the lower extremities. In the Walking and Leg Circulation Study, subjects with ABI of 0.90—0.99 had a greater mobility loss (HR:3.07; 95% CI: 1.21—7.84; $P = 0.0187$) and were more likely to become unable to walk for 6-min continuously (HR:5.88; 95% CI: 1.20—28.89; $P = 0.029$) compared with subjects with ABI of 1.00—1.09 during 5 years' follow-up [27]. These results would be an omen of ours.

A previous study showed that patients with diabetes had a high prevalence of PAD but had a low rate of diagnosis [28]. The presence of peripheral neuropathy blunted pain perception, which makes it difficult to determine the true early prevalence of PAD in diabetic patients using only symptoms or interviews. Although PAD is difficult to be identified early, detecting asymptomatic patients with borderline ABI is much more difficult, particularly in diabetes. Thus, many asymptomatic subjects with the significantly increased risk, not only of PAD but also of borderline ABI, do not have proper diagnosis, which necessitates early intervention for them.

There are several potential limitations to this study. First, we couldn't get the information of the clinical symptom of PAD. Second, we couldn't get the information about the duration of diabetes. Third, we couldn't collect toe-brachial index to assess the actual condition of patients with elevated ABI. Finally, although we made extensive statistical adjustments, unmeasured variables, like the duration of diabetes, and toe-brachial index, might still be present and bias our results toward an apparent lack of significant associations.

In conclusion, this study showed that not only abnormal ABI but also borderline ABI in diabetes were associated with a significantly higher risk for all-cause and cardiovascular mortality. Additionally, borderline ABI can be a predictor of the incidence of PAD. Early routine ABI screening to identify diabetic patients who are at high risk of premature all-cause death, cardiovascular death, and PAD could provide prognostic information that cannot be acquired from clinical and conventional risk factors alone.

Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

Authors' contributions

Chiharu Natsuaki, Toyoshi Inoguchi and Hajime Nawata designed the study and interpreted analysis. Chiharu Natsuaki, Toyoshi Inoguchi and Hajime Nawata obtained the funding. Chiharu Natsuaki did the administrative, technical, or material support. Chiharu Natsuaki performed data analysis and drafted the manuscript. Toyoshi Inoguchi reviewed/edited the manuscript for critical intellectual content. Hajime Nawata supervised this study. This is discussed with coauthors and agreement is reached prior to manuscript submission. Chiharu Natsuaki takes responsibility for the integrity of the data and the accuracy of the data analysis.

Acknowledgments

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2014.03.018.

References

[1] Suominen V, Uurto I, Saarinen J, Venermo M, Salenius J. PAD as a risk factor for mortality among patients with elevated ABI–a clinical study. Eur J Vasc Endovasc Surg 2010;39:316–22.

[2] McDermott MM. The magnitude of the problem of peripheral arterial disease: epidemiology and clinical significance. Cleve Clin J Med 2006;73(Suppl. 4): S2–7.

[3] Mueller T, Hinterreiter F, Luft C, Poelz W, Haltmayer M, Dieplinger B. Mortality rates and mortality predictors in patients with symptomatic peripheral artery disease stratified according to age and diabetes. J Vasc Surg; 2014 Jan 3 [ahead of print].

[4] Dieter RS, Tomasson J, Gudjonsson T, Brown RL, Vitcenda M, Einerson J, et al. Lower extremity peripheral arterial disease in hospitalized patients with coronary artery disease. Vasc Med 2003;8:233–6.

[5] Hennion DR, Siano KA. Diagnosis and treatment of peripheral arterial disease. Am Fam Physician 2013;88:306–10.

[6] Lin JS, Olson CM, Johnson ES, Whitlock EP. The ankle-brachial index for peripheral artery disease screening and cardiovascular disease prediction among asymptomatic adults: a systematic evidence review for the U.S. Preventive Services Task Force. Ann Intern Med 2013;159:333–41.

[7] Fowkes FG, Murray GD, Butcher I, Heald CL, Lee RJ, Chambless LE, et al. Ankle brachial index combined with Framingham risk score to predict cardiovascular events and mortality: a meta-analysis. J Am Med Assoc 2008;300:197–208.

[8] Heald CL, Fowkes FG, Murray GD, Price JF. Risk of mortality and cardiovascular disease associated with the ankle-brachial index: systematic review. Atherosclerosis 2006;189:61–9.

[9] Xu Y, Li J, Luo Y, Wu Y, Zheng L, Yu J, et al. The association between ankle-brachial index and cardiovascular or all-cause mortality in metabolic syndrome of elderly Chinese. Hypertens Res 2007;30:613–9.

[10] Zanati SG, Mouraria GG, Matsubara LS, Giannini M, Matsubara BB. Profile of cardiovascular risk factors and mortality in patients with symptomatic peripheral arterial disease. Clinics (Sao Paulo) 2009;64:323–6.

[11] Vicente I, Lahoz C, Taboada M, Laguna F, Garcia-Iglesias F, Mostaza Prieto JM. Ankle-brachial index in patients with diabetes mellitus: prevalence and risk factors. Rev Clin Esp 2006;206:225–9.

[12] Mostazaa JM, Manzanob L, Suarezc C, Fernandez C, Garcia de Enterria MM, Tirado R, et al. Different prognostic value of silent peripheral artery disease in type 2 diabetic and non-diabetic subjects with stable cardiovascular disease. Atherosclerosis 2011;214:191–5.

[13] Fan LC, Chen MY, Huang WC, Ho C, Chen PY, Huang JC, et al. Pulse pressure and Michigan neuropathy screening instrument are independently associated with asymptomatic peripheral arterial disease among type 2 diabetes community residents: a community-based screening program in Taiwan. Biomed J 2013;36:282–8.

[14] Brito-Zurita OR, Ortega-Lopez S, Lopez del Castillo-Sanchez D, Vazquez-Tellez AR, Ornelas-Aguirre JM. Ankle-brachial index associated with diabetic foot: case-control study. Cir Cir 2013;81:131–7.

[15] Brownrigg JR, Apelqvist J, Bakker K, Schaper NC, Hinchliffe RJ. Evidence-based management of PAD & the diabetic foot. Eur J Vasc Endovasc Surg 2013;45: 673–81.

[16] Dachun X, Jue L, Liling Z, Yawei X, Dayi H, Pagoto SL, et al. Sensitivity and specificity of the ankle-brachial index to diagnose peripheral artery disease: a structured review. Vasc Med 2010;15:361–9.

[17] Rooke TW, Hirsch AT, Misra S, Sidawy AN, Beckman JA, Findeiss LK, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline). Vasc Med 2011;16:452–76.

[18] Lilly SM, Qasim AN, Mulvey CK, Churchill TW, Reilly MP, Eraso LH. Non-compressible arterial disease and the risk of coronary calcification in type-2 diabetes. Atherosclerosis 2013;230:17–22.

[19] Diehm C, Allenberg JR, Pittrow D, Mahn M, Tepohl G, Haberl RL, et al. Mortality and vascular morbidity in older adults with asymptomatic versus symptomatic peripheral artery disease. Circulation 2009;120:2053–61.

[20] Kimura T, Morimoto T, Furukawa Y, Nakagawa Y, Shizuta S, Ehara N, et al. Long-term outcomes of coronary-artery bypass graft surgery versus percutaneous coronary intervention for multivessel coronary artery disease in the bare-metal stent era. Circulation 2008;118:S199–209.

[21] Geng YJ, Libby P. Progression of atheroma: a struggle between death and procreation. Arterioscler Thromb Vasc Biol 2002;22:1370–80.

[22] Kolluru GK, Bir SC, Kevil CG. Endothelial dysfunction and diabetes: effects on angiogenesis, vascular remodeling, and wound healing. Int J Vasc Med 2012;2012:918267.

[23] Syvanen K, Korhonen P, Partanen A, Aarnio P. Endothelial function in a cardiovascular risk population with borderline ankle-brachial index. Vasc Health Risk Manag 2011;7:97–101.

[24] Yan M, Mehta JL, Hu C. Lox-1 and obesity. Cardiovasc Drugs Ther 2011;25: 469–76.

[25] Henry RM, Kostense PJ, Spijkerman AM, Dekker JM, Nijpels G, Heine RJ, et al. Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. Circulation 2003;107:2089–95.

[26] Yoshimura T, Suzuki E, Egawa K, Nishio Y, Maegawa H, Morikawa S, et al. Low blood flow estimates in lower-leg arteries predict cardiovascular events in Japanese patients with type 2 diabetes with normal ankle-brachial indexes. Diabetes Care 2006;29:1884–90.

[27] McDermott MM, Guralnik JM, Tian L, Liu K, Ferrucci L, Liao Y, et al. Associations of borderline and low normal ankle-brachial index values with functional decline at 5-year follow-up: the WALCS (walking and leg circulation study). J Am Coll Cardiol 2009;53:1056–62.

[28] Maeda Y, Inoguchi T, Tsubouchi H, Sawada F, Sasaki S, Fujii M, et al. High prevalence of peripheral arterial disease diagnosed by low ankle-brachial index in Japanese patients with diabetes: the Kyushu Prevention Study for Atherosclerosis. Diabetes Res Clin Pract 2008;82:378–82.