cogent medicine

A reconciling criterion for early detection of asymptomatic PAD in HD patients

Paik Seong Lim, Yachung Jeng

Publisher: Cogent OA

Journal: *Cogent Medicine*

DOI: http://doi.org/10.1080/2331205X.2018.1469595

A reconciling criterion for early detection of asymptomatic PAD in HD patients

Paik Seong Lim[1,2] Yachung Jeng[3*]

[1] Division of Renal Medicine, Tungs' Taichung MetroHarbor Hospital, Taichung, Taiwan; [2] Department of Internal Medicine, Taipei Medical University, Taipei, Taiwan; [3] Translational Research Division, Medical Research Department, Taipei Veterans General Hospital, Taipei, Taiwan

*Corresponding author: Yachung Jeng, Translational Research Division, Medical Research Department, Taipei Veterans General Hospital, No.322, Sec. 2, Shipai Rd., Beitou Dist., Taipei City 112, Taiwan (R.O.C.). E-mail: yachungjeng@gmail.com

About the authors

Paik Seong Lim, M.D., PhD, is the chief of the Division of Renal Medicine at Tungs' Taichung MetroHarbor Hospital. He practices as a nephrologist for more than twenty years. His research focus is on issues related to chronic kidney disease medicine and involves in areas of molecular biology, biological chemistry, proteomics, and clinical epidemiology. He is very keen on striving for a better understanding on issues regarding nephrology and kidney disease patient long-term health care.

Yachung Jeng is a research fellow currently at the Medical Research Department of Taipei Veterans General Hospital. Her major is in biostatistics with an expertise in survival analysis and longitudinal data analysis. The authors collaborated as Dr. Jeng served in Tungs' Taichung MetroHarbor Hospital.

Photo of the author

Paik Seong Lim

Abstract

Background and aim: Peripheral arterial disease (PAD), an important manifestation of systematic atherosclerosis, is common in hemodialysis patients, while usually underdiagnosed because most patients were asymptomatic. Some evidence indicated that the currently accepted criteria of ankle-brachial index (ABI) for clinical diagnosis of PAD results in poor sensitivity in hemodialysis patients. Other evidence indicated a necessary on using a reconciling criterion of ABI in hemodialysis population. This study therefore examined the PAD incidence and medical conditions in a cohort of maintenance hemodialysis (HD) patients with intermediate ankle-brachial index (ABI, in 0.9-1), compared to those with high ABI (1-1.3) and with abnormal ABI (≤0.9). *Methods and results:* The Cox regression analysis on our cohort of hemodialysis patients showed that patients with intermediate ABI had significantly higher PAD incidence than those with high ABI (hazard ratio [95% confidence interval]: 4 [1.9-8.4]). The distribution of common medical conditions related to PAD, e.g., diabetes mellitus, cerebrovascular disease, body mass index, fasting blood sugar, and triglyceride, were significantly different between patients with intermediate ABI and high ABI, while no significant difference was observed between those with intermediate ABI and abnormal ABI. *Conclusions:* The results suggested an ABI cut-off point of 1, instead of the conventionally used 0.9, could be considered for earlier detection of asymptomatic PAD and atherosclerosis prevention in hemodialysis patients.

Keywords: asymptomatic, ankle-brachial index, hemodialysis, peripheral arterial disease.

Introduction

Peripheral arterial disease (PAD), an important manifestation of systematic atherosclerosis, is highly prevalent in hemodialysis (HD) patients (Lim et al., 2005; Jabbari et al., 2012). Nevertheless, PAD is usually underdiagnosed and undertreated or even delayed treatment, since most patients were asymptomatic. We are well aware that adverse outcomes such as cardiovascular diseases (Liu et al., 2009; Kuwahara et al., 2014) and vascular access failure (Chen et al., 2009; Singh et al., 2015) are correlated to PAD. Therefore, early identification of asymptomatic PAD cases in HD patients is crucial for nephrologists.

An ankle-brachial index (ABI) of 0.9 or less is the currently accepted criterion for clinical diagnosis of PAD (Chen et al., 2010; Garimella et al., 2012; Tendera et al., 2011). It is theoretically well known that a relaxing diagnostic threshold may result in a higher sensitivity. In addition, evidence indicated that the adverse-prognosis risk of dialysis patients with ABI above 0.9 could be further classified by ABI levels (Ono et al., 2003). With an idea of empirically validating, we retrospectively analyzed a cohort of HD patients to assess if using any lenient criterion of ABI could help predicting future risk of asymptomatic PAD in HD patients.

Methods

The medical records of a cohort of 275 outpatient HD patients were retrieved for eligibility identification and study data collection. The study observation period was designed as 2008/1/1~2013/9/30. The practice guideline was prepared following Ono et al [11]. Further detailed description on the cohort inclusion/exclusion criteria and on ABI surveillance implementation were included in Lim et al. (2016).

This study was approved by the institutional review board of (Tungs' Taichung MetroHarbor Hospital (TTMHH, No: 103020). The written informed consent was waived

because no invasive manipulations were involved in this study, the ABI surveillance and all study observations had been included in regular assessments in the HD unit of TTMHH since December 2006, and the data were analyzed anonymously.

The Cox regression were applied to assess the association between ABI level and the risk of PAD incidence whose baseline ABIs were all above 0.9 (ABI≤0.9 is the currently accepted criterion for PAD) (Chen et al., 2010; Garimella et al., 2012). Survival time was the duration from the date of study follow-up beginning to the first date when a subsequent ABI value was below 0.9. Patients who maintained at normal ABI levels throughout the follow-up were censored by the follow-up end. Chi-square test and ANOVA were applied as appropriate to evaluate the statistical association at a significant level of 0.05.

Results

Of the 217 eligible cases, 72 (33.18%) prevalent cases manifested a baseline ABI below 0.9 in January 2008, 47 (21.66%) incident cases had some subsequent ABI measurements below 0.9 during the study observation period, and 98 (45.16%) non-PAD cases whose ABI measurements maintained above 0.9 throughout the study observation period. During the follow-up (mean±standard deviation: 5±1.3 years), the annual PAD incidence in the first four years were 11.72%, 20.02%, 28.18%, and 37.04%.

In the incident cohort (n=145), conventional risk factors of PAD including old age, diabetes mellitus (DM), coronary artery disease (CAD)/cerebrovascular disease (CeVD), high body mass index (BMI), high triglyceride to cholesterol ratio (rTG), low level ratio of high density lipoprotein cholesterol (rHDL), and high fasting blood sugar (FBS) were associated with higher PAD incidence (see Table 1 for the detailed results). After adjusting all potential risk factors of PAD, an interesting result was found. Among HD patients with baseline ABI above 0.9, those with baseline ABI below 1 (≤ 1) manifested a significantly higher risk of

PAD incidence; the hazard increased to 4 times with 95% confidence interval [1.9, 8.4] and p-value 0.0003.

For an empirical exploration on biological plausibility, we evaluated the patterns of common medical conditions related to PAD patients among three groups of baseline ABI level (see Table 2). There was no significant difference in clinical correlates such as DM, CeVD, FBS, TG, rTG, and rHDL between patients with middle-level baseline ABI (>0.9 and ≤1) and with low-level baseline ABI (≤0.9). However, significant difference between patients with middle-level baseline ABI and with high-level baseline ABI (>1) was found in DM, CeVD, BMI, FBS, TG, and rTG. This indicated that even the conventional diagnosis criterion for PAD is ABI level of below 0.9, another accommodative cut-off point for early detecting of asymptomatic PAD should be considered for HD patients with ABI level above 0.9.

Discussion

In this retrospective cohort, a significantly higher incidence of PAD was observed in HD patients with baseline ABI between 0.9 and 1. Interestingly, for these patients the pattern of risk factors observed was similar to those HD patients having ABI <0.9. Clearly, we are aware that the value of 0.9 is somewhat arbitrary, as the ABI is a continuous variable that indicates the severity of the atherosclerotic process. A low normal value could be sometimes the sign of an early or moderate atherosclerotic process of vessels of lower limbs. Therefore, to allow earlier detection of asymptomatic PAD, a higher ABI cut-off point was suggested for maintenance HD patients. Evidence for such a view also comes from previous studies. Ono et al. (2003) found that HD patients with ABI in the range of 0.9-1 manifested significantly poor prognosis compared to patients with ABI in the range from 1 to 1.3. The abnormally stiff ankle arteries of HD patients due to medial arterial calcification might lead to more false negatives during ABI screening (Adragao et al., 2012).

Another interesting finding in this study was that patients with ABI in the range 0.9-1 manifested different prevalent rates of concomitant CAD and of CeVD at baseline. This group of patients appears to have similar CAD outcomes to patients with ABI in the range 1-1.3. In contrast, their CVD outcomes appear comparable to those with ABI in the range $\leq$ 0.9. It is well-known that atherosclerosis is a systemic process with variable expression in different vascular beds. Reasons for differential anatomic expression of atherosclerosis may involve the interplay between inflammation, shear stresses, flow characteristics, and other local factors. Accumulating recent evidence found that PAD patients had higher prevalence of concomitant cerebrovascular disease than coronary disease (Steg et al., 2007; CAPRIE Steering Committee, 1996; Abbott et al., 2001; Ovbiagele, 2009). Using data from the National Health and Nutrition Examination Survey, Ovbiagele (2009) found that only ABI $\leq$ 0.9 and 0.9-0.99 were significantly associated with presence of CVD as compared with the reference group (ABI in 1.10-1.29) after adjusted for related risk factors. In addition, patients with PAD have been shown to have an elevated prevalence of carotid stenosis (Kurvers et al., 2003; Long et al., 1999; Cheng et al., 1999). The risk of stroke rises with higher degree of symptomatic carotid stenosis (Jeng et al., 1994; De Weerd et al., 2010; Katsumata et al., 2007). In a study in Chinese patients, Cheng et al. (1999) found that moderate to severe carotid stenosis in 24.5% of patients with PAD but only 11% in patients suffering from CAD, suggesting a stronger link between CVD and PAD.

Since the arteries of the great toe are rarely involved in the calcification process, the toe-brachial index (TBI) is considered as an alternative for detection of PAD complicated with incompressible vessels. Recently, Matsuzawa and colleagues (2015) reported a superior sensitivity on TBI than on ABI (1 *vs*. 0.58) and concluded that "*screening for PAD using the ABI and TBI increased diagnostic efficiency in patients on HD*". In clinical practice, TBI measurements are more cumbersome, since features common in dialysis patients such as

deformed toenails, thickened toenails, repeated microtrauma or ulcer on toe, scabbed toes, and tinea pedis may render the measurements more time-consuming and technically difficult. Besides at present, there is lack of normative value from a large dialysis population that can define PAD in HD patients and hence there has been no consensus over the threshold of TBI.

Admittedly, a higher threshold theoretically resulted in higher sensitivity and also higher false positively rate. Several studies suggest that the ABI trend estimated from multiple ABI measurement is another predictor for outcomes relevant to PAD (Kuwahara et al., 2014; Chen et al., 2012; Feringa et al., 2007). An intensively multiple ABI surveillance following an initial one-shot examination with a higher threshold (ABI ≤ 1) could be a way to detection false positive cases in the initial examination, while the practical implementations needs further investigation. The unavailable data regarding the ascertainment of PAD by angiographic evaluation are a limitation of this retrospective cohort study. This impedes us to perform an ROC analysis, while efforts on such aspects will be pursued in future study. Hopefully, our findings may shed some new light on the issue.

Conclusion

Our findings imply that intensive surveillance, and advanced diagnostic workup should be considered for hemodialysis patients with ABI values within the lower normal range (0.9-1). Clearly, the sensitivity of currently used threshold needs to be re-evaluated in this vulnerable group of patients with advanced atherosclerosis.

References

Abbott, R. D., Rodriguez, B. L., Petrovitch, H., Yano, K., Schatz, I. J., Popper, J. S., ... & Curb, J. D. (2001). Ankle–brachial blood pressure in elderly men and the risk of stroke: the Honolulu Heart Program. Journal of clinical epidemiology, 54(10), 973-978.

Adragao, T., Pires, A., Branco, P., Castro, R., Oliveira, A., Nogueira, C., ... & Prata, M. M. (2012). Ankle-brachial index, vascular calcifications and mortality in dialysis patients. Nephrology Dialysis Transplantation, 27(1), 318-325.

CAPRIE Steering Committee. (1996). A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). The Lancet, 348(9038), 1329-1339.

Chen, S. C., Chang, J. M., Hwang, S. J., Tsai, J. C., Liu, W. C., Wang, C. S., ... & Chen, H. C. (2010). Ankle brachial index as a predictor for mortality in patients with chronic kidney disease and undergoing haemodialysis. Nephrology, 15(3), 294-299.

Chen, S. C., Chang, J. M., Hwang, S. J., Tsai, J. C., Wang, C. S., Mai, H. C., ... & Chen, H. C. (2009). Significant correlation between ankle-brachial index and vascular access failure in hemodialysis patients. Clinical Journal of the American Society of Nephrology, 4(1), 128-134.

Chen, S. C., Liu, W. C., Chang, J. M., Huang, J. C., Yang, T. K., Chen, H. C., ... & Su, H. M. (2012). Decrease in ankle-brachial index over time and cardiovascular outcomes in patients with hemodialysis. The American journal of the medical sciences, 344(6), 457-461.

Cheng, S. W., Wu, L. L., Lau, H., Ting, A. C., & Wong, J. (1999). Prevalence of significant carotid stenosis in Chinese patients with peripheral and coronary artery disease. Australian and New Zealand journal of surgery, 69(1), 44-47.

De Weerd, M., Greving, J. P., Hedblad, B., Lorenz, M. W., Mathiesen, E. B., O'Leary, D.

H., ... & Bots, M. L. (2010). Prevalence of asymptomatic carotid artery stenosis in the general population an individual participant data meta-analysis. Stroke, 41(6), 1294-1297.

Feringa, H. H. H., Karagiannis, S. E., Schouten, O., Vidakovic, R., van Waning, V. H., Boersma, E., ... & Poldermans, D. (2007). Prognostic significance of declining ankle-brachial index values in patients with suspected or known peripheral arterial disease. European journal of vascular and endovascular surgery, 34(2), 206-213.

Garimella, P. S., Hart, P. D., O'Hare, A., DeLoach, S., Herzog, C. A., & Hirsch, A. T. (2012). Peripheral artery disease and CKD: a focus on peripheral artery disease as a critical component of CKD care. American Journal of Kidney Diseases, 60(4), 641-654.

Jabbari, M., Jahromi, M. K., Bahar, N., Yousefi-far, E. S., Arabi, M., Asefi, N., & Mahmoudian, A. (2012). Prevalence of peripheral arterial disease in hemodialysis patients. Iranian journal of kidney diseases, 6(6), 441.

Jeng, J. S., Chung, M. Y., Yip, P. K., Hwang, B. S., & Chang, Y. C. (1994). Extracranial carotid atherosclerosis and vascular risk factors in different types of ischemic stroke in Taiwan. Stroke, 25(10), 1989-1993.

Katsumata, T., Nishiyama, Y., Yamaguchi, H., Otori, T., Nakamura, H., Tanaka, N., & Katayama, Y. (2007). Extracranial carotid plaque is increasing in Japanese ischemic stroke patients. Acta neurologica scandinavica, 116(1), 20-25.

Kurvers, H. A. J. M., Van der Graaf, Y., Blankensteijn, J. D., Visseren, F. L. J., Eikelboom, B. C., & SMART Study Group. (2003). Screening for asymptomatic internal carotid artery stenosis and aneurysm of the abdominal aorta: comparing the yield between patients with manifest atherosclerosis and patients with risk factors for atherosclerosis only. Journal of vascular surgery, 37(6), 1226-1233.

Kuwahara, M., Hasumi, S., Mandai, S., Tanaka, T., Shikuma, S., Akita, W., ... & Sasaki, S.

(2014). Rate of Ankle-Brachial Index Decline Predicts Cardiovascular Mortality in Hemodialysis Patients. Therapeutic Apheresis and Dialysis, 18(1), 9-18.

Lim, P. S., Chen, T. T., Yang, S. M., Chien, S. W., Kuo, Y. C., & Pai, M. A. T. (2005). Prevalence and clinical correlates of peripheral arterial disease in hemodialysis patients. Acta Nephrologica, 19(3), 113-120.

Lim, P. S., Jeng, Y., Wu, M. Y., Pai, M. A., Wu, T. K., & Chen, C. H. (2016). Role of Cilostazol Therapy in Hemodialysis Patients with Asymptomatic Peripheral Arterial Disease: A Retrospective Cohort Study. BioMed Research International, 2016. doi:10.1155/2016/8236903

Liu, J. H., Chang, C. C., Wang, S. M., Chou, C. Y., Yang, Y. F., Liu, Y. L., ... & Huang, C. C. (2009). Peripheral arterial disease and clinical risks in Taiwanese hemodialysis patients. Angiology.

Long, T. H., Criqui, M. H., Vasilevskis, E. E., Denenberg, J. O., Klauber, M. R., & Fronek, A. (1999). The correlation between the severity of peripheral arterial disease and carotid occlusive disease. Vascular Medicine, 4(3), 135-142.

Matsuzawa, R., Aoyama, N., & Yoshida, A. (2015). Clinical characteristics of patients on hemodialysis with peripheral arterial disease. Angiology, 66(10), 911-917.

Ono K, Tsuchida A, Kawai H, Matsuo H, Wakamatsu R, Maezawa A, et al. Ankle-brachial blood pressure index predicts all-cause and cardiovascular mortality in hemodialysis patients. J Am Soc Nephrol. 2003;14(6):1591-8.

Ovbiagele, B. (2009). Association of ankle–brachial index level with stroke. Journal of the neurological sciences, 276(1), 14-17.

Singh, K., Anderson, M. E., Pillai, A. K., & Kalva, S. P. (2015). Peripheral Arterial Disease in Hemodialysis Access. In Dialysis Access Management (pp. 181-196). Springer International Publishing.

Steg, P. G., Bhatt, D. L., Wilson, P. W., D'Agostino, R., Ohman, E. M., Röther, J., ... & Pencina, M. J. (2007). One-year cardiovascular event rates in outpatients with atherothrombosis. Jama, 297(11), 1197-1206.

Tendera, M., Aboyans, V., Bartelink, M. L., Baumgartner, I., Clément, D., Collet, J. P., ... & Heras, M. (2011). ESC Guidelines on the diagnosis and treatment of peripheral artery diseases. European heart journal, 32(22), 2851-2906.

Public interest statement

Peripheral arterial disease (PAD) is a common manifestation of systematic atherosclerosis in hemodialysis patients. In the population, however, it is often underdiagnosed because most patients were asymptomatic (i.e., without complaints for intermittent claudication, leg fatigue or cramping, muscles tightness or squeezing pain in hips, thighs or calves) even they have an abnormal ankle-brachial index (ABI) level (conventionally ≤0.9). By exploring the patterns of the PAD incidence and medical conditions among three groups of hemodialysis patients: intermediate group (ABI 0.9-1), abnormal group (ABI ≤0.9), and upper group (ABI >1), we found that the intermediate group had patterns significantly different from the upper group and non-significantly different from the abnormal group. Our findings imply that intensive surveillance, and advanced diagnostic workup or medical care regarding prevention on atherosclerosis progress should be considered for hemodialysis patients with ABI values within the lower normal range (0.90-1).

Table 1. The Cox regression analysis results for PAD incidence (*n*=145)

Models	Simple				Multiple			
Variables	**HR**	**95% CI**		**P-value**	**HR**	**95% CI**		**P-value**
Sex, male *vs.* female	1.234	0.668	2.28	0.502				
Age (years)	1.02	0.994	1.047	0.137	1.032	1.002	1.062	0.035 *
HD vintage (years)	0.998	0.935	1.065	0.957				
Comorbidity present, yes *vs.* no								
DM	3.048	1.649	5.634	0.0004 *				
HTN	1.576	0.807	3.081	0.183				
CAD or CeVD	2.166	1.164	4.029	0.015 *				
CAD	1.798	0.949	3.409	0.072				
CeVD	2.049	0.794	5.293	0.138				
CHF	1.071	0.4	2.863	0.892				
BMI (Kg/m^2)	1.096	1.008	1.191	0.031 *				
DBP (mmHg)	0.993	0.966	1.02	0.616				
SBP (mmHg)	1.006	0.992	1.021	0.391				
SBP > 155 *vs.* others (mmHg)	1.748	0.877	3.482	0.112	2.511	1.184	5.325	0.016 *
FBS (mg/dl)	1.012	1.006	1.019	0.0001 *				
TG (mg/dl)	1.003	1.001	1.006	0.008 *				
HDL-C (mg/dl)	0.981	0.961	1.002	0.078				
LDL-C (mg/dl)	1.001	0.992	1.01	0.883				
rTG	1.756	1.07	2.882	0.026 *	2.039	1.153	3.606	0.014 *
rHDL	0.027	0.001	0.774	0.035 *				
rLDL	0.746	0.05	11.06	0.831				
ABI value at entry, 0.9-1 *vs.* >1	3.57	1.795	7.092	0.0003 *	4	1.901	8.403	0.0003 *

Note: The dichotomous cutoff points (155 mmHg) for SBP were the third quartiles. Following listed the abbreviations. ABI: Ankle brachial pressure index. BMI: Body mass index. CAD: Coronary artery disease. CeVD: Cerebrovascular disease. CHF: Congestive heart failure. DBP: Diastolic blood pressure. DM: diabetes mellitus. FBS: Fasting blood sugar. HDL-C: High density lipoprotein cholesterol. HTN: Hypertension. LDL-C: Low-density lipoprotein cholesterol. rHDL: The ratio of high density lipoprotein cholesterol to total cholesterol. rLDL: The ratio of low density lipoprotein cholesterol to total cholesterol. rTG: The ratio of triglyceride to total cholesterol. SBP: Systolic blood pressure. TG: Triglyceride.

Table 2. The sample characteristics by baseline ABI levels. (*n* = 217)

Variables	Baseline ABI level			P-value[¶] (*n*=217)	P-value[†] (*n*=97)	P-value[‡] (*n*=145)
	≤0.9	>0.9, ≤1	>1			
	n(%)	*n*(%)	*n*(%)			
Sex						
Female	45(62.5)	11(44)	53(44.17)	0.039 *	0.107	0.9878
Male	27(37.5)	14(56)	67(55.83)			
DM						
No	20(27.78)	10(40)	84(70)	<.0001 *	0.255	0.0043 *
Yes	52(72.22)	15(60)	36(30)			
HTN						
No	15(20.83)	8(32)	42(35)	0.113	0.258	0.774
Yes	57(79.17)	17(68)	78(65)			
CAD/CeVD						
No	21(29.17)	15(60)	80(66.67)	<.0001 *	0.006 *	0.5235
Yes	51(70.83)	10(40)	40(33.33)			
CAD						
No	25(34.72)	19(76)	84(70)	<.0001 *	0.0004 *	0.5474
Yes	47(65.28)	6(24)	36(30)			
CeVD						
No	56(77.78)	19(76)	111(92.5)	0.0063 *	0.855	0.0137 *
Yes	16(22.22)	6(24)	9(7.5)			
CHF						
No	65(91.55)	22(91.67)	105(88.24)	0.7259	0.986	0.6266
Yes	6(8.45)	2(8.33)	14(11.76)			
	mean±SD	*mean±SD*	*mean±SD*			
Age (years)	64.71±11.08	64.64±10.81	61.42±12.2	0.1243	0.979	0.2229
HD vintage (years)	4.27±4.28	4.5±5.23	4.11±4.5	0.9189	0.831	0.7072
BMI (Kg/m2)	23.94±4.03	24.17±4.06	22.45±3.22	0.008 *	0.803	0.0222 *
DBP (mmHg)	73.15±13.01	75.48±11.21	78.78±11.37	0.0067 *	0.428	0.1873
SBP (mmHg)	135.82±25.21	133.72±23.38	139.65±21.55	0.354	0.716	0.2194
FBS (mg/dl)	123.24±48.16	124.24±56.37	103.47±37.43	0.0041 *	0.932	0.0233 *
TG (mg/dl)	179.51±107.4	205.08±204.43	134.98±82.16	0.0024 *	0.428	0.0052 *
HDL-C (mg/dl)	40.38±13.52	47.17±16.65	49.28±15.5	0.0004 *	0.048 *	0.5473
LDL-C (mg/dl)	96.63±29.69	91.13±32.73	92.82±34.67	0.6727	0.446	0.826

rTG	0.9±0.7	0.94±0.57	0.75±0.49	0.0076 *	0.859	0.0315 *
rHDL	0.24±0.08	0.27±0.12	0.3±0.1	0.0001 *	0.11	0.2496
rLDL	0.55±0.1	0.51±0.14	0.54±0.11	0.2146	0.087	0.2181

Note: See the footnote of Table 1 for abbreviations. The last three columns were p-values for comparisons among three groups by baseline ABI level (indicated by ¶), between groups of baseline ABI levels below 0.9 and in 0.9-1 (indicated by †), and between groups of baseline ABI levels above 1 and in 0.9-1 (indicated by ‡). Chi-square test and F test was respectively applied to categorical variables and continuous variables.