Angiology
61(6) 524-529

DOI: 10.1177/0003319710371614
http://ang.sagepub.com

Study on Unrecognized Peripheral Arterial Disease (PAD) by Ankle/Brachial Index and Arterial Comorbidity in Catania, Sicily, Italy

Salvatore Santo Signorelli, MD[1], Massimiliano Anzaldi, MD[1], Valerio Fiore, MD[1], Stefano Catanzaro, MD[1], Massimo Simili, MD[1], Benedetto Torrisi, Assistant Professor[2], and Sergio Neri, MD[1],

Abstract

Peripheral arterial disease (PAD) is under diagnosed and early diagnosis decreases consequences. We screened unrecognized PAD focusing on arterial co-morbidities. In the 3412 subjects, screened from 10 general practices in the city of Catania (Sicily, Italy), ankle brachial index (ABI) measurements were performed. An ABI $\leq$0.9 was considered as valid in diagnosing PAD. ABI value $\leq$0.9 was found in 2.3%, and a significant rate of carotid stenosis was also found Echocardiographic markers left ventricular diameter (LVD) >55 mm, interventricular septum (IVS) >11 mm, left ventricular diastolic volume (LVDV) was found > 100 ml), and ejection fraction (EF) was <50% were found with high frequency in those with ABI $\leq$0.9. Unrecognized PAD is lower compared with other findings but our prevalence resulted higher than other prevalence previously found by other study performed in Italy. Unrecognized PAD shows significant arterial co-morbidities and the ABI is a useful method to screen asymptomatic PAD.

Keywords

peripheral arterial disease, epidemiology, ankle brachial index, comorbidity

Introduction

Peripheral arterial disease (PAD) represents an independent indicator of future individual risk of cardiovascular disease ([CVD]; myocardial infarction [AMI], transient ischemic attack [TIA], or stroke).[1-5] Early identification of PAD is crucial both to antagonize asymptomatic progression of damage in the peripheral arterial bed and consequently decrease the risk of CVD-related events. Many studies have focused on epidemiology of PAD by using different methods such as clinical questionnaires, treadmill test, and ankle–brachial index (ABI). The ABI is considered a reliable method to diagnose PAD and to evaluate global cardiovascular risk.[6-16] This simple and easy method was suggested to general practitioners to raise awareness about PAD and obtain early diagnosis of this disease.[17-21] To date epidemiological findings on PAD were discordant and ranged between 2% and 3% and up to more than 15% in different general or hospitalized populations.[22-25] A study analyzed this issue, considering a population of south Italy, and Brevetti and coworkers[26] have highlighted the low prevalence of PAD in this population and this study confirmed that this population was less prone to CVD. We estimated the prevalence of unrecognized PAD in Catania, Sicily, Italy. We also estimated arterial comorbidity (carotid and cardiac) and risk factors for CVD in patients diagnosed with PAD.

Materials and Methods

Participants (n = 9100), who were listed in the recorded files of 10 general practitioners, were invited to undergo a visit at the outpatient clinic and 3332 (37.49%) attended. The general practitioners asked to collaborate in the study were selected from different districts of Catania, Sicily, Italy. Men and women between the ages of 30 and 80 were considered. Patients with known PAD were not considered for the study. All the participants received an invitation letter informing them of the date of the visit, the reason for the invitation, and that they were to undergo a noninvasive evaluation of an arterial condition. The study was carried out in 3 steps. Step 1: all participants that accepted this invitation were asked to complete a specific medical questionnaire regarding the

[1] Department of Internal Medicine and Systemic Disease, Section of Internal Medicine and Vascular Medicine, University of Catania, Italy
[2] Department of Economy, Faculty of Economy University of Catania (Italy)

Corresponding Author:
Salvatore Santo Signorelli, Department of Internal Medicine and Systemic Disease, Section of Internal and Vascular Medicine, c/o Ospedale Garibaldi Centro, Piazza S Maria di Gesù,7, 95123, Catania, Italy
Email: ssignore@unict.it

cardiovascular risk factors (ie, diabetes mellitus, hypercholesterolemia, arterial hypertension, smoke, weight, height to measure body mass index; Table 1). We considered those participants that used anti-diabetic drugs as diabetic and those with a systolic arterial pressure $\geq$ 140 mm Hg and/or a diastolic blood pressure $\geq$ 80 mm Hg as hypertensive patients. Participants that used statins or other lipid-lowering drugs were considered as hyperlipidemic and those participants who stopped smoking for 3 months as past smokers. The arterial pressure on the posterior or on the anterior tibial artery (when the posterior artery was not detectable) was measured using an ultrasound (US) device with a 8-mHz pencil probe (Microdop 8-mHz CE 0459; Sonomed, Rome, Italy). The pressure in the brachial artery was also measured using the US probe. Three consecutive measurements on the peripheral arteries and brachial artery were performed and the mean of the highest measures were calculated. Measurement was performed after 5 minutes of supine position and acclimatization in the visit room. The ratio between the mean highest values of the peripheral blood pressure and the brachial pressure was calculated, thus defining the ABI for each participant. In our study, an ABI $\leq$ 0.9 was diagnosed with PAD whereas the participants with an ABI > 0.9 were considered healthy controls. This study was designed to focus on the prevalence of unrecognized PAD as diagnosed by an ABI value of $\leq$ 0.9. In other studies, participants with an ABI value > 1.4 and those who show incompressibility of arteries were considered. The US were performed by specialized and experienced physician with a long training period in a medical vascular unit. Among the ABI values, we found an inter- and intra-observer variability of less than 0.05; so the differences were not clinically relevant. Step 2: patients with an ABI value $\leq$ 0.9 were asked to attend a US evaluation on the carotid arteries and the peripheral arteries using an echo color Doppler device (Mylab 70; Esaote Ind, Genova, Italy) to assess the intima-media thickness (IMT) > 0.9 mm and the presence of atheromatous plaques in the carotid arteries. Step 3: patients with an ABI value $\leq$ 0.9 were also asked to undergo the echocardiography examination to assess the myocardial condition and the following markers were considered: the diastolic left ventricular diameter (DLVD) >55 mm, the diameter of interventricular septum (IVS) >11 mm, the left ventricular diastolic volume (LVDV) >100 mL, and the ejection fraction (EF) <55%.

Data Analysis

The statistical analysis was performed to verify the relationship between each of the various risk factors (type II diabetes, arterial hypertension, dyslipidemia, smoking, number of cigarettes/day, BMI, and waist–hip ratio [WHR]) with the ABI value, and the Pearson test was applied. We found a direct relationship between the ABI and arterial hypertension ($R = .177$, *P /it> < .03), with the BMI (*$R = .440$, $P < .00001$), and WHR ($R = .276$, $P < .003$; Table 4). Moreover, to verify the cumulative effect of the cardiovascular risk factors, a multiple regression model (MRL) was applied. The estimated model shows both the regression coefficient and the *t* test to indicate the statistical relevance of the regression coefficients and furthermore the statistical test to verify the adaptability of the multiple linear function.

The descriptive analysis is expressed with the average $\pm$ standard deviation of different variables for each patient, with the reported predominant percentages. The odds ratio [OR] and confidence intervals (CIs) were also calculated. The analysis was carried out using SPSS 10.1 Windows. A P value < .05 was considered significant.

Table 1. Demographic and Clinical Characteristics of the Screened Population

	Controls	PAD
n	3332	80 (2.34%)
Age, years	54.4 $\pm$ 12.6	62.7 $\pm$ 10.53
Males, n (%)	1312 (38.5%)	52 (65%)
Females, n (%)	2020 (61.5%)	28 (35%)
Smokers, n (%)	680 (22.2)	48 (60%)
Nonsmokers, n (%)	1184 (61.3)	20 (25%)
Past smokers, n (%)	508 (16.5)	12 (15%)
Type 1 diabetes, n (%)	12 (0.4)	
Type 2 diabetes, n (%)	200 (6.5)	24 (30%)
Hypertension, n (%)	1016 (33.1)	40 (50%)
Dyslipidemia, n (%)	908 (29.6)	40 (50%)
BMI	26.3 $\pm$ 5.3	27.3 $\pm$ 3.9
WHR	92.5 $\pm$ 12.6	97.2 $\pm$ 10.3
Right leg pressure, mm Hg		130.9 $\pm$ 26
Left leg pressure, mm Hg		123.9 $\pm$ 27.59
ABI	1.18 $\pm$ 0.10	0.81 $\pm$ 0.11

Abbreviations: ABI, ankle–brachial index; BMI, body mass index; PAD, peripheral arterial disease; WHR, waist–hip ratio.

Results

The demographic and medical characteristics of the general population are outlined in Table 1. In our study, we found an ABI value $\leq$ 0.9 in 80 out of 3412 patients, obtaining a total prevalence of PAD of 2.3% (mean ABI 0.81 $\pm$ 0.11). Of 80, 52 (65%) patients with PAD were males and 28 (35%) were females; the mean age was 61.3 $\pm$ 9.7 years old. Of 80, 24 (30%) patients had type 2 diabetes, 40 (50%) had arterial hypertension, and 40 (50%) had hyperlipidemia. Of 80, 48 (66.7%) were smokers and 16 (22.2%) were ex-smokers; 56 (77.8%) of those patients showed a BMI higher than 25, and 48 (66.7%) showed a WHR higher than that of the cutoff level for their gender (>102 males and >88 females). The higher prevalence of the ABI value $\leq$0.9 in age ranges (30-39, 40-49, 50-59, 60-69, 70-79, and >79 years) of the PAD was found in the third (40 [50%]of 80 patients). The Rose questionnaire was found as positive to predict the intermittent claudication in 32 of 80 patients with an ABI value $\leq$0.9 and in was negative in 48 of the 80 patients. Conversely only in 72 of the control participants the questionnaire was found as positive and in the other controls it was negative to diagnose the intermittent claudication.

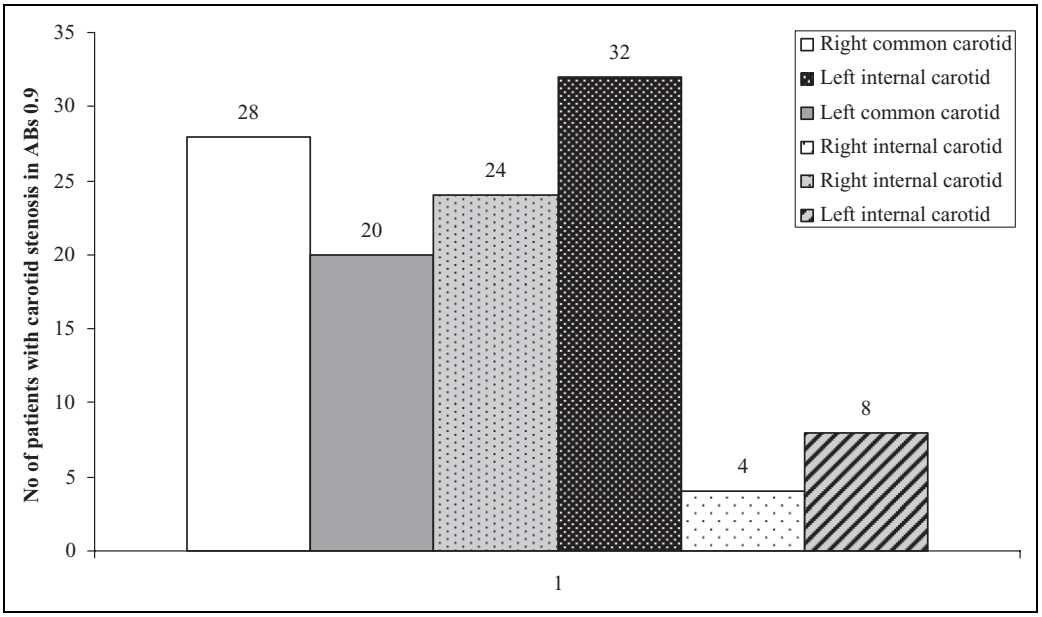

Figure 1. Number of the patients with the ABI $\leq$ 0.9 and stenosis of the carotid arteries.

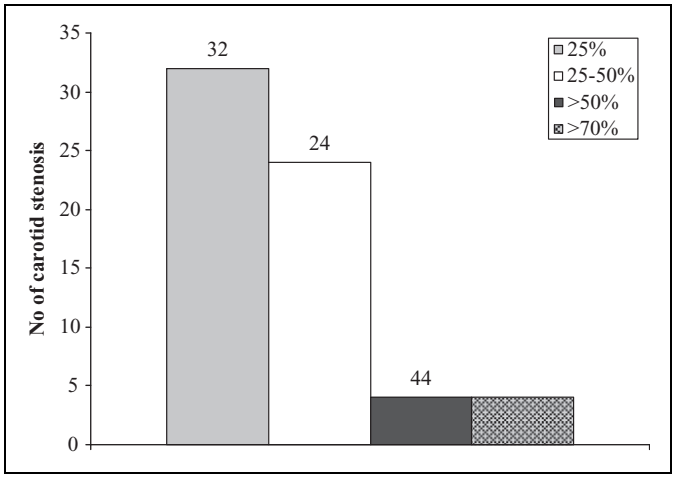

Figure 2. Number of patients with the ABI $\leq$ 0.9 and lesser or more severe degree of the arterial stenosis of the carotid artery.

Carotid Artery Comorbidity

Of 80, 76 (95.0%) patients (ABI < 0.9) showed an IMT > 0.9 mm. Of these patients, 60 (75.1%) showed the presence of atherosclerotic plaque detected by the US. We also took into account the stenosis degree on the carotid lumen (<25%, 25%-50%, >50%, and >75%) according to the NASCET (North American Symptomatic Carotid Endoarterectomy Trial) criteria.[27] The carotid stenosis >25% was found in 32 (40%)of 80 of the patients with ABI $\leq$ 0.9, and stenosis ranging between 25% and 50% was found in 24 (30%)of 80, whereas stenosis >50% was found in 4 (5.0%) of 80 patients and only 4 (5%) of 80 showed carotid stenosis >75% (Figures 1 and 2).

Cardiac Comorbidity

Among the echocardiographic parameters, in 64 of 80 patients, we found that 8 patients (12.5%) showed an LVD greater than 55 mm, 32 patients (50%) had an IVS greater than 11 mm, 36 patients (56.3%) showed an LVDV greater than 100 mL, and 8 patients (12.5%) showed an EF lower than 50% (Figure 3).

Risk for PAD (Univariate and Multivariate Analysis)

Considering the single risk factor in the univariate analysis (Table 2), we found a relationship between the ABI, the arterial hypertension ($R = .177$, $P < .03$) the BMI ($R = .440$, $P < .00001$), and the WHR ($R = .276$, $P < .003$). The relationship between all the risk factors with the ABI that was considered the dependent variable is shown in Table 3. Based on this analysis, only the BMI was statistically relevant. The R^2 value was .022 (95% CI 0.010-0.034, $P < .001$). Table 3 also shows the coefficient and the relative statistical P values. Furthermore, in the population with PAD, we found a high OR for type II diabetes (OR 6.154), smoke (OR 4.758), and those who smoked more than 20 cigarettes per day (OR 5.541), as well as for a pathological value of BMI (OR 1.631) and for an increased WHR (OR 1.605).

Discussion

In our study, we found a lower prevalence of the unrecognized PAD compared to the findings of other large previous studies carried out both in Northern Europe and in the United States, where results ranged from 1.6% to 7.7%. The prevalence of

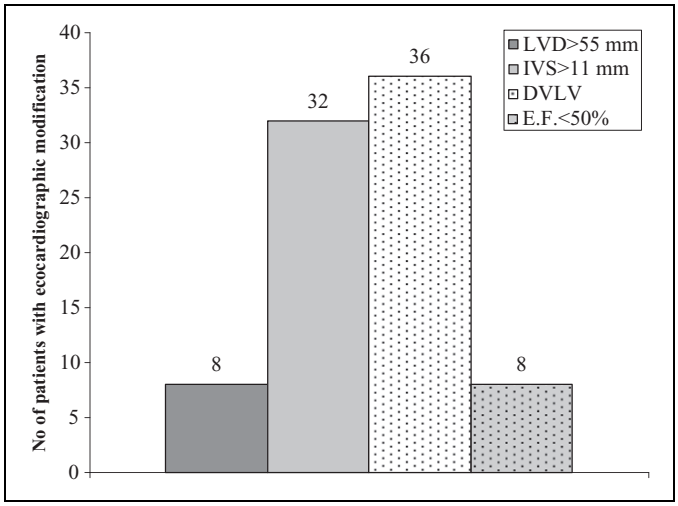

Figure 3. Number of patients with ABI $\leq$ 0.9 that present cardiac dysfunction through echocardiographic marker measurement. LVD indicates left ventricular diastole; IVS, interventricular septum; DVLV, diastolic volume of the left ventricle; EF, ejection fraction.

Table 2. The Correlation Coefficient Between the Cardiovascular Risk Factors and ABI Shows the Relevance and Statistical Significance of the Relationship Between the Risk Factors for Cardiovascular Diseases and the ABI Value $\leq$0.9

Type 2 diabetes	Pearson correlation	−.050
	Significance (2-tailed)	.062
	N	80
Hypertension	Pearson correlation	.117[a]
	Significance (2-tailed)	.030
	N	80
Dyslipidemia	Pearson correlation	.235[a]
	Significance (2-tailed)	.036
	N	80
Smoke	Pearson correlation	−.093
	Significance (2-tailed)	.413
	N	80
Smoke >20/day	Pearson correlation	.190
	Significance (2-tailed)	.195
	N	48
BMI	Pearson correlation	.440[b]
	Significance (2-tailed)	.000
	N	80
WHR	Pearson Correlation	.276[a]
	Significance (2-tailed)	.013
	N	80

[a, b] Correlation coefficient between the cardiovascular risk factors and ABI
Abbreviations: BMI, body mass index; WHR, waist−hip ratio.

unrecognized PAD probably could to be raised whether we could also take into account those listed patients with known diagnosed PAD. The wide range in terms of prevalence in the different studies performed in other countries both in the North of Europe and in the United States derives from the different diagnostic methods of this disease, screening methods, and from the characteristics of the population (age, hospitalized or not, observational survey, etc). In fact, in the Edinburgh study,[28] the prevalence of intermittent limping was 4.6% while data from a survey performed in Sweden[29] showed a prevalence of 7.0%. A study performed in Germany,[30] based on the measurement of ABI, has shown high prevalence of PAD, which ranged between 19.8% and 16.8%, respectively, in men and in women. In the Swiss Atherothrombosis Survey,[31] the prevalence of symptomatic PAD was 3.7% and an additional 2.7% of asymptomatic PAD was found. Data from Lacroiix and colleagues[25] have shown that the overall prevalence of undiagnosed PAD in the hospitalized patients was 29.3%, but the presence of intermittent limping was only 3%. The study performed by Brevetti and colleagues[26] considering a large population of a southern region of Italy (Campania) has shown lower prevalence of the PAD compared to data from studies performed in other countries of Europe. Our results on prevalence of unrecognized PAD conversely were found a higher than results of this interesting study that was concerned a large population of south of Italy. In fact, in our study, we found the prevalence of PAD was 2.5%. However, based on our results, we agree with the point of view postulated by Brevetti and colleagues[26] concerning a low prevalence of unrecognized PAD in southern Italy compared to other countries in northern Europe, and in turn these findings could be considered an evidence of the low prevalence of CVDs in population living in the countries bordering the Mediterranean sea.[32,33] Our data strongly support that the population of Italy, and particularly those people living in southern Italy, is less prone to atherosclerotic diseases and specifically to PAD compared to the European or American populations but on the other hand we have also demonstrated that in these patients a high arterial and cardiac comorbidity can exist. Furthermore, we found the higher prevalence of PAD in fifth range (50-59 years) and sixth range (60-69 years) of age, and these data can be of further proof to confirm the common appearance of PAD in the elderly individuals. We believe that our results agree with the conclusive data suggested by the recent review on the PAD.[34] that stated PAD is a characteristic disease of older individuals and also it is not an isolated disease but shows many systemic effects, and finally patients affected by PAD have serious risk of severe cardiovascular consequences. Moreover, the authors highlighted again that the ABI is effective in the early diagnosis of PAD and helping to reduce the morbidity and mortality risk of CVD in these patients.

Concluding Remarks

We would like to stress the evidence on high prevalence of the PAD in the decades ages ranged between 50 and 69 years by taking into consideration 2 questions that concern the increase in the average life span and the consequent increase in the number of people potentially susceptible to PAD. Furthermore, we found that type 2 diabetes, smoking, BMI, and WHR were associated with PAD, and we underline the fact that these factors can determine a high risk of PAD, as demonstrated by the OR values reported. In patients with unrecognized PAD

Table 3. Multiple Regression Test to Estimate the Relation Between the Cardiovascular Risk Factors and the ABI Value[a]

	Coefficient	Standard Error	Stat *t*	*P* Value	CI 95%	
Type 2 diabetes	−0.013	0.033	−0.393	.069	−0.079	0.053
Hypertension	0.024	0.030	0.814	.418	−0.035	0.084
Dyslipidemia	0.056	0.033	1.696	.094	−0.010	0.123
Smoke	−0.007	0.043	−0.157	.875	−0.093	0.079
Smoke >20	−0.030	0.046	−0.654	.051	−0.122	0.062
BMI	0.022	0.006	3.567	.001	0.010	0.034
WHR	−0.004	0.002	−1.584	.118	−0.008	0.001

Abbreviations: BMI, body mass index; WHR, waist−hip ratio.
[a] The ABI is considered dependent variable.

(as diagnosed by the ABI $\leq$ 0.9) a relevant prevalence of arterial comorbidity for carotid and heart disease was found. In these patients, we found that a significant prevalence of atherosclerotic plaques endowed on the carotid arteries, and we consider this as a noteworthy finding in this study. We also found high percentages of modified echocardiographic remarks, and these data were consistent to prove a concomitant and asymptomatic heart disarrangement in the patients with unrecognized PAD. It is well known that patients with PAD are at high risk of CVD, and the studies have shown a high frequency of concomitant manifestation of atherothrombotic diseases (myocardial infarction, angina pectoris, stroke, TIA, carotid, and coronary revascularization). In the Italian study on prevalence of PAD, patients diagnosed with PAD showed a high risk of cardiac disease (OR 4.47; CI 2.1-9.4) and also cerebrovascular problems (OR 2.86; CI 0.6-14.6). As we know, the US technique represents a useful and specific diagnostic tool to detect the presence and/or progression of arterial remodelling,[35] and it is usually now applied in noninvasive vascular laboratories. The early diagnoses both of arterial remodelling and of the early evidence of the atherosclerotic plaque represent crucial aspects in assessing the ischemic risk and in preventing more aggressive progression of arterial damage using correct pharmacological treatments. Finally, we want to underline again that the ABI is a easy and useful test to achieve 2 effective goals both to diagnose unrecognized PAD and to start a critical need for global arterial evaluation for this kind of patients.

Declaration of Conflicting Interests

The author(s) declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research and/or authorship of this article.

References

1. Criqui MH, Langer RD, Fronek A, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992;326(6):381-386.
2. McKenna M, Wolfson S, Kuller L. The ratio of ankle and arm arterial pressure as an independent predictor of mortality. *Atherosclerosis*. 1991;87(2-3):119-126.
3. Smith GD, Shipley MJ, Rose G. Intermittent claudication, heart disease risk factors, and mortality. The Whitehall Study. *Circulation*. 1990;82(6):1925-1931.
4. Leng LC, Lee AJ, Fowkes FG, et al. Incidence, natural history and cardiovascular events in symptomatic and asymptomatic peripheral arterial disease in the general population. *Int J Epidemiol*. 1996;25(6):1172-1131.
5. Newman AB, Siscovick DS, MAnolio TA, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. *Circulation*. 1993;88(3):8837-8834.
6. 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. *Atheroscl Thromb Vasc Biol*. 1999;19(3): 538-535.
7. Reich LM, Heiss G, Boland LL, Hirsch AT, Wu K, Folsom AR. Ankle-brachial index and hemostatic markers in the Atherosclerosis Risk in Communities (ARIC) study cohort. *Vasc Med*. 2007; 12(4):267-273.
8. Feringa HH, Karagiannis SE, Schouten O, et al. Prognostic significance of declining ankle-brachial index values in patients with suspected or known peripheral arterial disease. *Eur J Vasc Endovasc Surg*. 2007;34(2):206-212.
9. Luo YY, Li J, Xin Y, Zheng LQ, Yu JM, Hu DY. Risk factors of peripheral arterial disease and relationship between low ankle brachial index and mortality from all-cause and cardiovascular disease in Chinese patients with hypertension. *J Hum Hypertens*. 2007;21(6):461-466.
10. Sprynger M, Bassotte C, Verhaeghe R. The ankle-brachial pressure index and a standardized questionnaire are easy and useful tools to detect peripheral arterial disease in non-claudicating patients at high risk. *Int Angiol*. 2007;26(3):239-244.
11. Allison MA, Hiatt WR, Hirsch AT, Coll JR, Criqui MH. A high ankle-brachial index is associated with increased cardiovascular disease morbidity and lower quality of life. *J Am Coll Cardiol*. 2008;51(13):1292-1298.
12. Criqui MH, Minomiya JK, Wingard DL, Ji M, Fronek A. Progression of peripheral arterial disease predicts cardiovascular disease

morbidity and mortality. *J Am Coll Cardiol*. 2008;52(21): 1743-1744.
13. Wild SH, Byrne CD, Smith FB, Lee AJ, Fowkes FG. Low ankle-brachial pressure index predicts increased risk of cardiovascular disease independent of the metabolic syndrome and conventional cardiovascular risk factors in the Edinburgh Artery Study. *Diabets Care*. 2006;29(3):637-642.
14. Weatherley BD, Nelson JJ, Heiss G, et al. The association of the ankle-brachial index with incident coronary heart disease: the Atherosclerosis Risk In Communities (ARIC) study, 1987-2001. *BMC Cardiovasc Disord*. 2007;7:3.
15. Murabito JM, Evans JC, Larson MG, Nieto K, Levy D, Wilson PW. Framingham Study. The ankle-brachial index in the elderly and risk of stroke, coronary disease, and death: the Framingham Study. *Arch Intern Med*. 2003;163(16):1939-1942.
16. Agnelli G, Cimminiello C, Meneghetti G, Urbinati S. the polyvascular Atherothrombosis Observational Survey (PATHOS) Investigators. Low ankle-brachial index predicts an adverse 1-year outcome after acute coronary and cerebrovascular events. *J Thromb Haemost*. 2006;4(12):2599-2606.
17. Mohler ER 3rd, Treat-Jacobson D, Reilly MP, et al. Utility and barriers to performance of the ankle-brachial index in primary care practice. *Vasc Med*. 2004;9(4):253-260.
18. Hirsh AT, O'Donnell M, Eikelboom JW. Beyond unfractionated heparin and warfarin: current and future advances. *Circulation*. 2007;116(5):2086-2094.
19. Muthu C, Chu JJ, Le Heron C, Roake JA, Lewis DR. Patient awareness of risk factors for peripheral vascular disease. *Ann Vasc Surg*. 2007;21(4):433-447.
20. Clark CE. Screening for peripheral vascular disease. *Br J Gen Pract*. 2007;April 57; (537):311-5.
21. Nicolaï SP, Kruidenier LM, Rouwet EV, et al. Pocket Doppler and vascular laboratory equipment yield comparable results for ankle brachial index measurement. *BMC Cardiovasc Disord*. 2008;8:26.
22. Hirsch AT, Halverson SL, Treat-Jacobson D, et al. The Minnesota Regional Peripheral Arterial Disease Screening Program: toward a definition of community standards of care. *Vasc Med*. 2001; 6(2):87-96.
23. Ramos R, Quesada M, Solonas P, et al. Prevalence of symptomatic and asymptomatic peripheral arterial disease and the value of ankle-brachial index to stratify cardiovascular risk. *Eur J Vasc Endovasc Surg*. 2009;38(3):305-311.
24. Ostchenga Y, Paulose-Ram R, Dillon CF, Gu Q, Hughes JP. Prevalence of peripheral arterial disease and risk factors in persons aged 60 and older: data from the National Health and Nutrition Examination Survey 1999-2004. *J Am Ger Soc*. 2007;55(4):583-589.
25. Lacroix P, Aboyanis V, Vorononin D, Le Guyader A, Cautrés M, Laskar M. High prevalence of undiagnosed patients with peripheral arterial disease in patients hospitalised for non-vascular disorders. *Int J Clin Pract*. 2008;62(1):59-64.
26. Brevetti G, Oliva G, Silvestro A, Scopacasa F, Chiariello M. Peripheral Arteriopathy and Cardiovascular Events (PACE) Study Group. Prevalence, risk factors and cardiovascular comorbidity of symptomatic peripheral arterial disease in Italy. *Atherosclerosis*. 2004;175(1):131-138.
27. Moneta GL, Edwards JM, Chitwood RW, et al. Correlation of North American Symptomatic Carotid Endarterectomy Trial (NASCET) angiographic definition of 70% to 99% internal carotid artery stenosis with duplex scanning. *J Vasc Surg*. 1993;17(1): 152-157.
28. Sigvant B, Wijber-Hedman K, Berqvist D, et al. A population-based study of peripheral arterial disease with special focus on critical limb ischemia and sex differences. *J Vasc Surg*. 2007; 45(6):1185-1191.
29. Diehm C, Schuster A, Allenberg JR, et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. *Atherosclerosis*. 2004;172(1):95-105.
30. Hayoz D, Bounameaux H, Canova CR. Swiss Atherothrombotic survey: a field report on the occurrence of symptomatic and asymptomatic peripheral arterial disease. *J Int Med*. 2005; 258(3):238-243.
31. Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD, Fowkes FG. Inflammatory, haemostatic, and rheological markers for incident peripheral arterial disease. *Eur Heart J*. 2007;28(3): 354-362.
32. de Lorgeril M, Sales P, Martin JL. Mediterranean diet, traditional risk factors and the rate of cardiovascular complication of myocardial infarction: the final report of the Lyon Diet heart Study. *Circulation*. 1999;Feb 16;99(6):733-5.
33. Ciccarone E, Di Castelnuovo A, Salcuni M. A high-score Mediterranean dietary pattern is associated with a reduced risk of peripheral arterial disease in the Italian patients with type 2 diabetes. *J Thromb Haemost*. 2003;1(18):1744-1752.
34. Stehouwer DA, Clement D, Davidson C. the EFIM Vascular Medicine Working Group. Peripheral arterial disease: a growing problem for the internist. *Eur J Internal Med*. 2009;20(2): 132-138.
35. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Study Group. *N Engl J Med*. 1999;340(1):14-22.