The Egyptian Heart Journal (2011) 63, 7–12

Egyptian Society of Cardiology

The Egyptian Heart Journal

www.elsevier.com/locate/ehj
www.sciencedirect.com

ORIGINAL ARTICLE

Associations of symptomatic or asymptomatic peripheral arterial disease with all-cause mortality and cardiovascular mortality

Eid M. Daoud [a], Mahmoud M. Ramadan [a,*], Nader El-Shahhat [a], Ayman A. Abd El-Samad [a], Nader El-Malkey [b], Sherif A. Sakr [a], Insaf Bassam [b], Hazem Hakeem [b], Asmaa Eneen [b], Adel El-Badrawy [c]

[a] *Department of Cardiology, Faculty of Medicine, Mansoura University, Egypt*
[b] *Department of Internal Medicine, Faculty of Medicine, Mansoura University, Egypt*
[c] *Department of Radiology, Faculty of Medicine, Mansoura University, Egypt*

Received 15 October 2010; accepted 21 November 2010
Available online 14 October 2011

KEYWORDS

Peripheral arterial disease;
Ankle brachial index;
All-cause mortality;
Cardiovascular mortality

Abstract *Background:* To investigate the rate of all cause and cardiovascular mortality in patients with symptomatic or asymptomatic peripheral arterial disease (PAD) compared to those without PAD.

Methods and results: All the subjects were inpatients at high risk of atherosclerosis and enrolled from February to November, 2006. A total of 320 were followed up until an end-point (death) was reached or until February 2010. The mean follow-up time was 37.7 ± 1.5 months. Compared with non-PAD, PAD patients had significantly higher rates of hypertension, diabetes mellitus, and smoking ($P < 0.01$). Those with symptomatic and asymptomatic PAD had a much higher all cause (37.5% and 23.0% vs. 12.1%) and cardiovascular mortality (18.8% and 13.8% vs. 6.7%) compared to those without PAD ($P < 0.001$). The symptomatic PAD patients were 1.831 times (95% CI: 1.222–2.741) as likely to die as those without PAD, and 1.646 times (95% CI: 1.301–2.083) in asymptomatic PAD patients after adjusting for other factors. Those with symptomatic or

* Corresponding author. Address: Department of Cardiology, Specialized Medicine Hospital, Mansoura University, Egypt. Tel.: +20 111 5811 548.
E-mail address: amamod2020@yahoo.com (M.M. Ramadan).

Peer review under responsibility of Egyptian Society of Cardiology.
doi:10.1016/j.ehj.2011.08.022

asymptomatic PAD were more than twice as likely to die of CVD as those without PAD (RR: 2.248, 95% CI: 1.366–3.698 and RR: 2.105, 95% CI: 1.566–2.831, respectively).
Conclusions: PAD was associated with a higher all cause and cardiovascular mortality whether or not PAD is symptomatic.

1. Introduction

Peripheral arterial disease (PAD) caused by atherosclerotic occlusion of leg arteries is an important manifestation of systemic atherosclerosis. The prevalence of PAD is variable in different reports,[1–6] but the average age-adjusted prevalence of PAD is approximately 12%.[7] Many trials have shown that PAD was associated with considerable general and cardiovascular (CV) morbidity and mortality. PAD prevalence of 25% was reported in patients with coronary artery disease (CAD).[8] One US study estimated PAD prevalence of more than 5 million adults. Patients with critical PAD face an annual mortality rate of 25%, which is overwhelmingly due to myocardial infarction and ischemic stroke.[9] However, only few patients present typical intermittent claudication which can be diagnostic of PAD. Ankle-brachial index (ABI), a ratio of ankle systolic blood pressure (SBP) to brachial systolic pressure, is widely used in clinical practice to assess the potency of the lower arterial system and to screen for PAD. The ABI threshold of 0.9 has a sensitivity of 95% and a specificity of 100% compared with angiography.[10] In 2006, our team firstly began to investigate the baseline characteristics of PAD patients, who were followed-up for a mean period of 3 years to find the relationship between mortality and symptomatic or asymptomatic PAD in Egyptian population.

2. Methods

2.1. Study design and participants

This study was designed in 2006 to investigate the risk factors for PAD in Egyptian population, and the relationship between mortality and symptomatic or asymptomatic PAD. All the subjects were hospitalized patients over 35 years old with 2 or more CV risk factors and enrolled from Mansoura University Hospital and Mansoura Specialized Medicine Hospital from February to November 2006. Risk factors included smoking, diabetes mellitus (DM), hypertension, dyslipidemia, stroke and history of CAD. Exclusion criteria included severe heart failure, liver cell failure, renal failure or cancer. Finally, a population of 372, aged $\geqslant$35 years, including 197 men and 175 women who had complete baseline data were included in the cohort. They were followed up until an end-point (death) was reached or until February 2010. The mean follow-up duration was 3 years (37.7 months) Informed consent was obtained from all the participants.

2.2. ABI measurement

Doppler ultrasound was used to measure SBP on bilateral brachial position, tibial and dorsal pedal arteries after at least 5 minutes of rest in the supine position. The Doppler probe was used at a frequency of 5 MHz. The left or right ABI is the ratio of the pressure on the left or right dorsal or posterior tibial arteries to the higher brachial pressure. An ABI $\leqslant$ 0.9 in either leg was considered as evidence of PAD.[11]

2.3. Diagnosis and classification of PAD

The diagnosis of PAD was assessed by ABI measurements, and the ABI $\leqslant$ 0.9 was used to diagnose PAD. Symptomatic PAD was defined as those whose ABI $\leqslant$ 0.9 and with a typical intermittent claudication. Asymptomatic PAD was those whose ABI $\leqslant$ 0.9 and without a typical intermittent claudication. Non-PAD was those with 0.9 $<$ ABI $\leqslant$ 1.40.

2.4. Identification of all-cause and CV death

Death was identified by hospitals' records or by contacting the participants' families. Further causes of death were investigated by using medical record and informant interviews. All materials were reviewed independently to confirm the cause of death.

2.5. Statistical analysis

Values of continuous variables, such as age, SBP, diastolic blood pressure, plasma glucose, total cholesterol, triglycerides, high-density lipoprotein-cholesterol, and low-density lipoprotein-cholesterol were expressed as mean ± standard deviation of mean. Categorical variables were expressed as percentages. All the participants were classified into symptomatic PAD, asymptomatic PAD or Non-PAD group. Independent-samples ANVOA and the chi-square tests were used to compare continuous and categorical differences at baseline, respectively.

Kaplan–Meier model was employed to calculate the cumulative mortality rate from all-cause and CV causes among the three groups. Cox regression model was used to estimate the independent association between PAD and all-cause and CV mortality compared with Non-PAD, after adjusting for age, gender, smoking, CAD, hypertension, stroke, DM, dyslipidemia and medications. A P-value of <0.05 was considered significant. All analyses were performed with SPSS (Statistics Package for Social Science) version 16.0.

3. Results

A total of 372 participants with available baseline data were enrolled in the cohort; of these, 96 participants (26.0%) were diagnosed as PAD by ABI (19 patients with symptomatic PAD and 77 with asymptomatic PAD) and 276 constituted the non-PAD group (the baseline characteristics of all subjects in the beginning of study are shown in Table 1). During a mean follow-up time of 37.6 ± 1.5 months, 52 (14%) of all the subjects were lost during the follow-up because of the changes of telephone number or family address. Among those

Table 1 The characteristics of all patients at baseline in the beginning of study.

Baseline characters	Symptomatic PAD (n = 19)	Symptomatic PAD (n = 77)	Non-PAD (n = 276)	P-value
Age (years)	71.8 ± 8.7	71.6 ± 9.7	65.2 ± 11.1	< 0.001
Gender (male, %)	52.3	48.5	54.4	< 0.05
CAD (%)	64.8	60.6	52.3	< 0.001
Hypertension (%)	87.6	77.7	70.4	< 0.001
SBP (mmHg)	146.3 ± 25.8	142.4 ± 24.4	138.7 ± 22.9	< 0.001
DBP (mmHg)	80.3 ± 14.1	80.8 ± 12.6	80.6 ± 12.8	< 0.005
DM (%)	60.1	46.4	35.5	< 0.001
Plasma glucose (mmol/L)	6.9 ± 3.0	6.7 ± 3.0	6.4 ± 2.8	< 0.05
Dyslipidemia (%)	57.9	43.2	41.6	< 0.01
TC (mmol/L)	4.7 ± 1.2	4.7 ± 1.2	4.6 ± 1.1	> 0.05
TG (mmol/L)	1.7 ± 1.2	1.8 ± 1.5	1.7 ± 1.1	> 0.05
LDL-C (mmol/L)	2.8 ± 0.9	2.7 ± 0.8	2.7 ± 1.5	> 0.05
HDL-C (mmol/L)	1.1 ± 0.3	1.2 ± 0.4	1.2 ± 0.4	< 0.05
Stroke (%)	61.7	51.9	38.3	< 0.001
Smoking (%)	48.7	40.6	38.0	< 0.05

Abbreviations: CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; HDL-C, high-density lipoprotein-cholesterol.

missing subjects, three were in the symptomatic PAD group, 12 in the asymptomatic PAD group, and 37 in the non-PAD group.

After careful calculation, the missing subjects did not significantly affect the major results of this study. There were 320 subjects with complete data after 3 years of follow-up. The patients with PAD were older than those without PAD (71.8 ± 8.7 for symptomatic and 71.6 ± 9.7 for asymptomatic PAD vs. 65.2 ± 11.1 for non-PAD, $P < 0.001$). Compared with non-PAD, PAD patients with or without symptom had significantly higher morbidity of CAD, hypertension, DM, dyslipidemia, stroke or smoking (all $P < 0.01$). Of the 320 participants (16 with symptomatic PAD; 65 with asymptomatic PAD and 239 without PAD) who had complete follow-up data; 50 of them died including 28 patients who died of CV causes. The number of all-cause deaths and CV deaths were 6 and 3, 15 and 9, 29 and 16 in symptomatic PAD, asymptomatic PAD and non-PAD group, respectively. The 3-year all cause mortality in PAD patients was 26%. Fig. 1 is a flow chart which shows the cascade of events since the inclusion of patients at baseline until the end of the study.

Table 2 demonstrates the incidence of all-cause and CV mortalities among the three groups after 3 years follow-up. Those with symptomatic PAD had a significant highest ($P < 0.001$) all cause (37.5%) and CV (18.8%) mortalities among the three groups. The mortality was still significantly higher in PAD patients without symptom (23% for all-cause, 13.8% for CV causes) than in those without PAD (12% for all-cause, 6.7% for CV causes; $P < 0.001$).

As shown in Figs. 2A and 2B, all cause and CV mortalities were compared according to gender among the three groups. No significant differences of mortalities were found in male or female PAD patients with or without symptom; but men had slightly higher mortality than women in the non-PAD group (14.2% vs. 10.0% for all cause mortality and 7.8% vs. 5.1% for CVD mortality, $P < 0.05$).

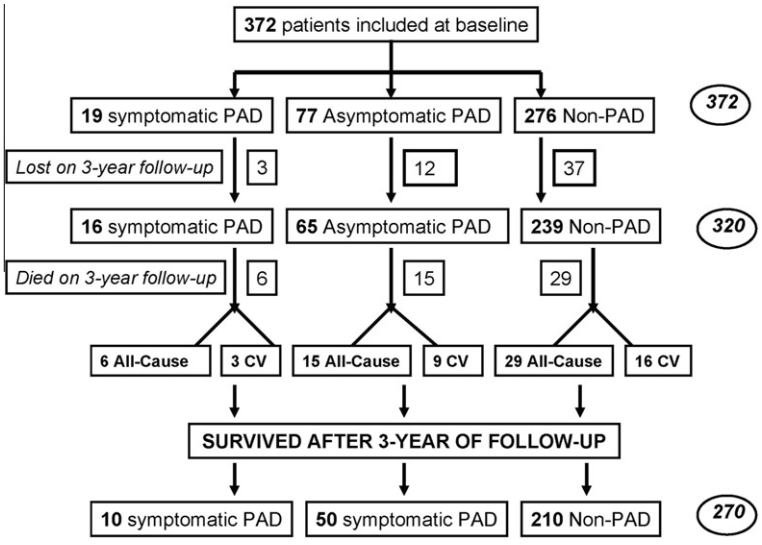

Figure 1 Flow chart showing the cascade of events since the inclusion of patients at baseline until the end of the study.

Table 2 The incidence of all-cause and cardiovascular mortalities among the three groups after 3 years follow-up.

Mortality	Symptomatic PAD (n = 16)	Asymptomatic PAD (n = 65)	Non-PAD (n = 239)	P-value
All-cause	6 (37.5%)	15 (23.0%)	29 (12.1%)	<0.001
Cardiovascular	3 (18.8%)	9 (13.8%)	16 (6.7%)	<0.001

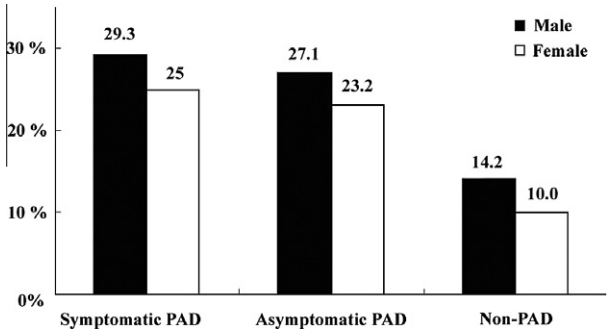

Figure 2A All cause mortalities among the three groups after 3 years follow-up.

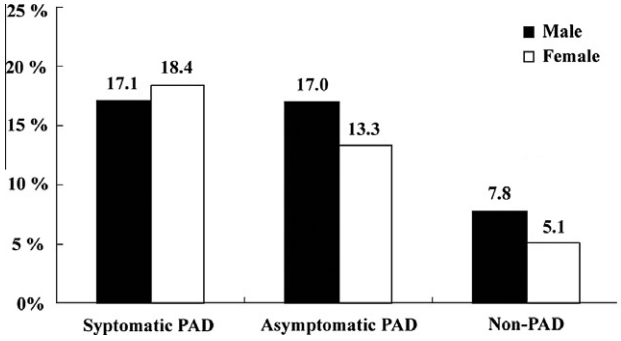

Figure 2B Cardiovascular mortalities among the three groups after 3 years follow-up.

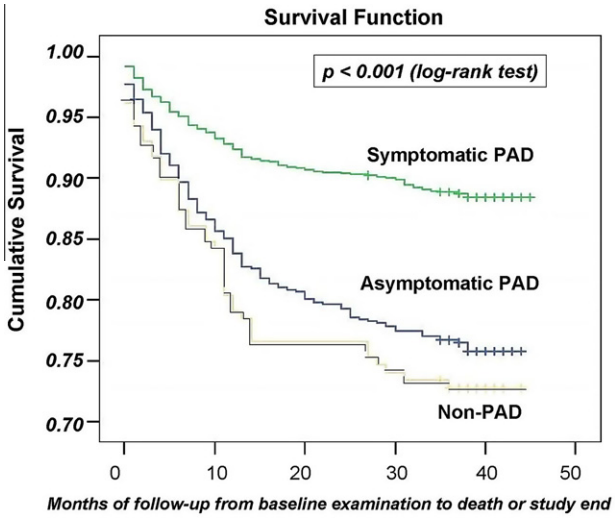

Figure 3A Univariate Kaplan–Meier curves for subjects among the three groups for all-cause mortality after 3 years follow-up.

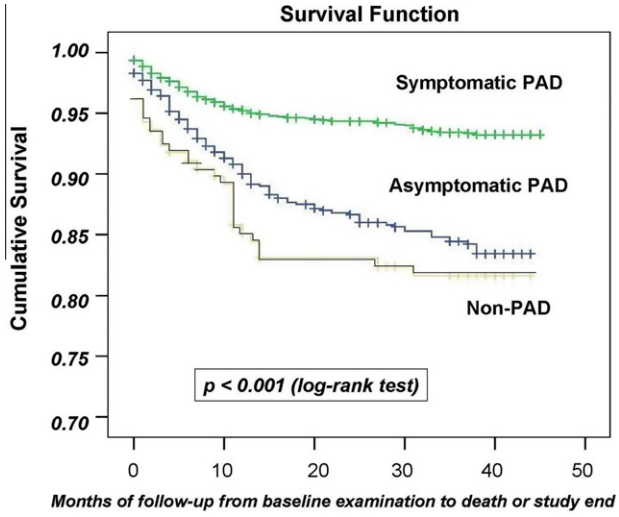

Figure 3B Univariate Kaplan–Meier curves for subjects among the three groups for cardiovascular mortality after 3 years follow-up.

Figs. 3A and 3B illustrate the survival distribution of the three groups for all-cause and CVD mortality, respectively. The cumulate survival rates in patients with symptomatic or asymptomatic PAD were significantly lower than those without PAD (log-rank test $P < 0.001$).

Figs. 4A and 4B showed the adjusted relative risk (RR) of all cause and CV mortality in the three groups. The symptomatic PAD patients were 1.831 times (95% CI: 1.222–2.741) as likely to die as those without PAD, and 1.646 times (95% CI: 1.301–2.083) in asymptomatic PAD patients after

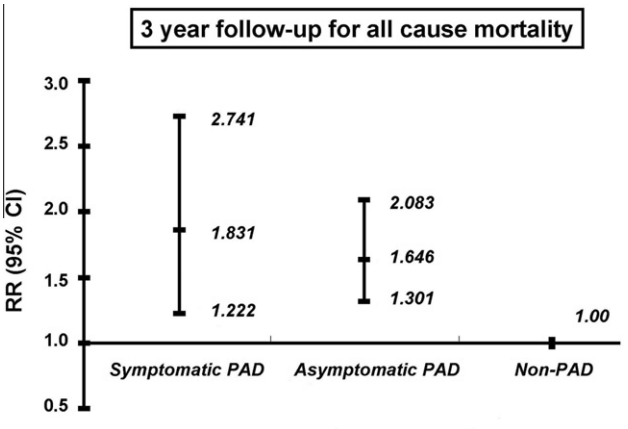

Figure 4A Relative risks of all cause mortality (adjusted for gender, age, smoking, CAD, hypertension, stroke, DM, dyslipidemia and medications for those diseases) after 3 years follow-up.

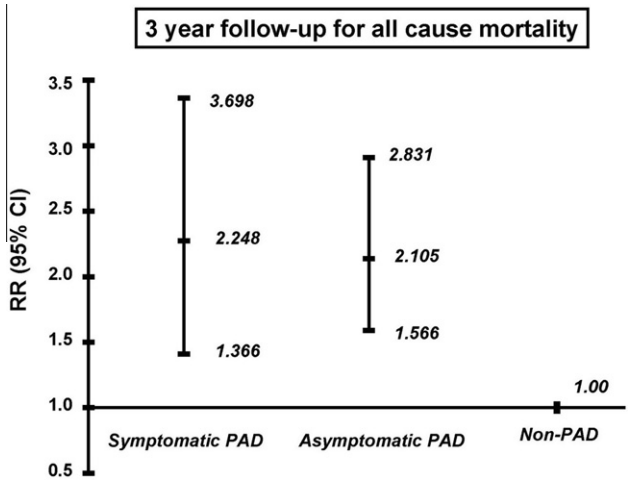

Figure 4B Relative risks of cardiovascular mortality (adjusted for gender, age, smoking, CAD, hypertension, stroke, DM, dyslipidemia and medications for those diseases) after 3 years follow-up.

adjusting for age, gender, smoking, CAD, hypertension, stroke, DM, dyslipidemia and medications for those diseases. Those with symptomatic or asymptomatic PAD had more than twice as likely to die of CV causes as those without PAD (RR: 2.248, 95% CI: 1.366–3.698 and RR: 2.105, 95% CI: 1.566–2.831, respectively) after adjusting for other factors.

4. Discussion

Atherosclerosis is a systemic disease, which is considered the leading cause of death and waste of health resources in adults worldwide. Recently, physicians tried to find a predictor to early identify atherosclerotic diseases. Epidemiological and clinical trials have proved that PAD is widely accepted as an indicator for generalized atherosclerosis, but PAD is quite often asymptomatic in older adults. However, trials showed that both symptomatic and asymptomatic patients with PAD have an increased mortality compared to those without PAD.[12] Many trials have also shown ABI as a marker of PAD which predicts CV and overall mortality. Stoffers et al.[13] reported that up to three-quarters of patients with PAD were asymptomatic, but our results showed that four-fifths of PAD patients are without typical symptoms.

The patients with PAD (whether or not symptomatic) were older and more likely to have CAD, hypertension, DM, dyslipidemia, stroke or smoking than those without PAD at baseline (Table 1), a result similar to Newman's former report.[5] During the 3 years follow-up, there was a significantly increased tendency on all-cause mortality from non-PAD, asymptomatic PAD to symptomatic PAD; and the same applies to CV mortality (Table 2). The all cause mortality was 37.5% in patients with symptomatic PAD, 23.0% in patients with asymptomatic PAD, and 12.1% in patients without PAD. Thus, the all cause mortality in patients with PAD was 60.5%. Diehm *et al* reported that the 3 years all cause mortality was 10.9% in patients with PAD.[14] Our figures were much higher, because our subjects were inpatients at high risk of atherosclerosis. However, all those data highlighted that PAD patients are at a very high risk of death. Diehm et al.[15] further showed that the 5 years all cause mortality was 24.1% in patients with symptomatic PAD, 19.2% in patients with asymptomatic PAD (low ABI), and 9.5% in patients without PAD; while others reported that the estimated five-year mortality in patients with PAD was 30%.[16,17]

No significant gender difference was found regarding all cause mortality and CV mortality in symptomatic and asymptomatic PAD groups; but male patients seemed to have a higher mortality than females. A striking increase in all cause and CV mortality was seen in PAD groups, especially in the symptomatic PAD one (Figs. 3A and 3B).

After adjusting for age, gender, smoking, CAD, hypertension, stroke, DM, dyslipidemia and medications by Cox regression model, the symptomatic PAD patients were 1.831 times as likely to die as those without PAD, and 1.646 times in asymptomatic PAD patients. The risk of death in patients with symptomatic or asymptomatic PAD was more than 2-fold higher than that of non-PAD.

In this study, we showed that the patients with asymptomatic PAD were still at high risk of death. Moreover, our research and other reports proved that a low ABI is a strong predictor of mortality during follow-up; even in patients with no clinical symptoms of PAD.[18,19] A recent meta-analysis also showed that the measurement of the ABI may improve the accuracy of CV risk prediction beyond the Framingham risk score.[20]

Although PAD is highly prevalent, physician awareness and detection of this disease is low[8,21], perhaps the high rate of asymptomatic disease is the most important reason.[13] ABI was regarded as indicator of mortality for many years; but in the whole strategy of atherosclerosis risk detection, less attention has been paid to the measurement of ABI, and – therefore – the presence of PAD has been underscored or not recognized.[21,22] Hence screening for PAD should be performed routinely in all elderly patients and in the general population who are at increased risk of subsequent CV events.

Evaluation is now required for the potential of incorporating ABI measurement into CV prevention programs. PAD should be aggressively treated just as coronary artery disease.[23] All those measures should be applied to identify PAD in order to reduce mortality.

There are several limitations to our study. Firstly, the duration of follow-up is only 3 years, so that further study should be done. Secondly, 14% of the subjects were lost during the follow-up due to the changes of telephone number or home address. If not, we could get more precise results. Thirdly, all the subjects were inpatients at high risk of atherosclerosis; so that our study cannot represent the general population in Egypt.

References

1. Schroll M, Munck O. Estimation of peripheral atherosclerotic disease by ankle blood pressure measurements in a population study of 60-year old men and women. *J Chronic Dis* 1981;**34**:261–9.
2. Meijer WT, Hoes AW, Rutgers D, Bots ML, Hofman A, Grobbee DE. Peripheral arterial disease in the elderly: the Rotterdam Study. *Arterioscler Thromb Vasc Biol* 1998;**18**:185–92.
3. Fowkes FGR, Housley E, Cawood EHH, Macintyre CCA, Ruckley CV, Prescott RJ. Edinburgh Artery Study: prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 1991;**20**:384–92.

4. Newman AB, Sutton-Tyrrell K, Rutan GH, Locher J, Kuller LH. Lower extremity arterial disease in elderly subjects with systolic hypertension. *J Clin Epidemiol* 1991;**44**:15–20.
5. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, et al.. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. *Circulation* 1993;**88**:837–45.
6. Zheng ZJ, Sharrett AR, Chambless LE, Rosamond WD, Nieto FJ, Sheps DS, et al.. Associations of ankle-brachial index with clinical coronary heart disease, stroke and preclinical carotid and popliteal atherosclerosis: the Atherosclerosis Risk in Communities (ARIC) Study. *Atherosclerosis* 1997;**131**:115–25.
7. Criqui MH, Denenberg JO, Langer RD, Fronek A. The epidemiology of peripheral arterial disease: importance of identifying the population at risk. *Vasc Med* 1997;**2**:221–6.
8. Hasimu B, Li J, Nakayama T, Yu J, Yang J, Li X. Ankle brachial index as a marker of atherosclerosis in Chinese patients with high cardiovascular risk. *Hypertens Res* 2006;**29**:23–8.
9. Dormandy JA, Heeck L, Vig S. The fate of patients with critical leg ischemia. *Semin Vasc Surg* 1999;**12**:142–7.
10. Fowkes FG. The measurement of atherosclerotic peripheral arterial disease in epidemiological surveys. *Int J Epidemiol* 1988;**17**:248–54.
11. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL. Society for Cardiovascular Angiography and Interventions; Society for Vascular Medicine and Biology; Society of Interventional Radiology; ACC/AHA Task Force on Practice Guidelines Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease; American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; Vascular Disease Foundation. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; Trans-Atlantic Inter-Society Consensus; and Vascular Disease Foundation. *Circulation* 2006;**113**:463–654.
12. Rockson SG, Cooke JP. Peripheral arterial insufficiency: mechanisms, natural history, and therapeutic options. *Adv Intern Med* 1998;**43**:253–77.
13. Stoffers HE, Rinkens PE, Kester AD, Kaiser V, Knottnerus JA. The prevalence of asymptomatic and unrecognized peripheral arterial occlusive disease. *Int J Epidemiol* 1996;**25**:282–90.
14. Diehm C, Lange S, Darius H, Pittrow D, von Stritzky B, Tepohl G, et al.. Association of low ankle brachial index with high mortality in primary care. *Eur Heart J* 2006;**27**:1743–9.
15. Diehm C, Allenberg JR, Haberl R, Harald Darius, Matthias Tepohl, Gerhart Tepohl, et al.. High all-cause mortality in patients with peripheral arterial disease in primary care: five-years results of the getabi study. *Circulation* 2007;**116**:833–41.
16. Dieter RS, Chu WW, Pacanowski JP, McBride PE, Tanke TE. The significance of lower extremity peripheral arterial disease. *Clin Cardiol* 2002;**25**:3–10.
17. Weitz JI, Byrne J, Clagett CP, Farkouh ME, Porter JM, Sackett DL, et al.. Diagnosis and treatment of chronic arterial insufficiency of the lower extremities: a critical review. *Circulation* 1996;**94**:3026–49.
18. 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**:1440–4.
19. Newman AB, Shemanski L, Manolio TA, Cushman M, Mittelmark M, Polak JF. Ankle-arm index as a predictor of cardiovascular disease and mortality in the cardiovascular health study. *Arterioscler Thromb Vasc Biol* 1999;**19**:538–45.
20. Ankle Brachial Index Collaboration. Ankle brachial index combined with Framingham Risk Score to predict cardiovascular events and mortality: a meta-analysis. *JAMA* 2008;**300**:197–208.
21. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, et al.. Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 2001;**286**:1317–24.
22. Heidrich H, Wenk R, Hesse P. Frequency of asymptomatic peripheral arterial disease in patients entering the department of general and internal medicine of a general-care hospital. *Vasa* 2004;**33**:63–7.
23. Grundy SM, Cleeman JI, Merz CN, Brewer Jr HB, Clark LT, Hunninghake DB. National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation* 2004;**110**:227–39.