Cent. Eur. J. Med. • 9(5) • 2014 • 601-608
DOI: 10.2478/s11536-013-0309-8

Central European Journal of **Medicine**

Association of the thickness of carotid intima-media complex and ancle brachial index with coronary disease severity

Research Article

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Received 22 September 2012; Accepted 5 March 2014

Abstract: Our aim was to establish the association of carotid intima-media thickness (CIMT) and ankle-brachial index(ABI) with the severity of coronary artery dissease (CAD). The study enrolled 150 examinees and divided them into two groups. The patients with stenotic changes in the coronary artery, constituted the first group (CP)(n=100); the second group consisted of the examinees without CAD - control goup (CG) (n=50). The following methods were used in the study: Color Doppler sonography of the carotid arteries, ABI, calculation of SCORE risk and coronary angiography. Results. The number of coronary blood vessels affected by atherosclerosis was significantly higher with the increase of CIMT, CV risk score, and waist-hip ratio by one measurement unit: CIMT by 0.729; $p<0.05$; CV risk score by 0.033; $p<0.05$; and waist- hip ratio by 3.182; $p<0.01$. With each increase of ABI value by one measurement unit, the number of involved blood vessels dropped by 0.844; $p<0.05$. Conclusions. Our results demonstrated that reduced ABI value, increased CIMT and number of plaques in the carotid arteries were in correlation with the severity of coronary artery disease.

Keywords: *Carotid intima-media thickness • Ankle-brachial index • Coronary artery disease • SCORE risk*

1. Introduction

Cardiovascular (CV) diseases, especially coronary artery disease (CAD), represent a huge health problem due to their causing wide spread early invalidity, frequent hospitalizations, and premature fatal outcomes. CV disease often have an asymptomatic latent period, providing the chance for early detection and use of prevention and treatment measures. Disease detection in its preclinical asymptomatic phase, using simple but precise methods, is the principal goal of modern cardiology. Color Duplex ultrasound enables measurement of the carotid intima-media thickness (CIMT), morphological evaluation of the atheromatous plaque, and consequential functional changes in the carotid hemodynamics. The CIMT of the common carotid arteries is a good indicator of systemic atherosclerosis [1]. Research trials suggest that CIMT is also a marker of risk for future atherosclerotic cardiovascular events [2].

The ankle-brachial index (ABI) is also a non-invasive marker of atherosclerosis. The index represents the ratio of the blood pressure in ankle arteries to the pressure in the brachial artery. ABI value is the simplest indicant of occlusive changes in lower leg arteries and the basic non-invasive method for diagnosis of peripheral occlusive disease and surveillance after revascularization procedures, with 79-95% sensitivity

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and 95-100% specificity [3]. Moreover, abnormal ABI values are a powerful predictor of CV events in people with already present CV disease. In asymptomatic individuals, a low ABI is associated with increased CV risk, and it may improve prognostic accuracy of the widely used Framingham score [4].

2. Aim of the paper

Our aim was to establish the association of CIMT and ABI with the severity of CAD.

3. Examinees

The study enrolled 150 examinees divided into two groups. The patients with CAD and stenotic changes in the coronary blood vessels (verified invasively), referred to the Institute „Niška Banja“ for specialized rehabilitation, constituted the first group – coronary patients (CP) (n=100); the second group consisted of the examinees without anamnestic and medical data suggestive of coronary disease – control group (CG) (n=50).

4. Method of work

The following methods were used in the study.

4.1. Color Doppler sonography of the carotid arteries

We used Color Doppler sonography of the magistral blood vessels in the neck using the machine EsaoteBiomedica, My Lab60 Xvision, with 4-13 MHz multi-frequency linear probe. Intraluminal lesions were documented using B-mode imaging and defined as CIMT and plaques as focal intimal protuberances. CIMT in the posterior wall of the common carotid artery, 2 cm away from the bifurcation apex, in the region without focal changes, was measured. We analyzed bilaterally longitudinal images of the common carotid artery, arteria carotis interna, and arteria carotis externa, with stenosis diameter determination and analysis of plaque properties.

4.2. ABI measurement

ABI was measured in a traditional way, supination after a 5 minutes' rest with a cuff placed at the junction of the middle and lower third of the lower leg (or the upper arm for superior extremities), with inflation up to suprasystolic values, interrupting the blood flow. Flow reappearance was detected using a multifrequency ultrasound probe (4-13 MHz), representing the value of systolic pressure in the studied extremity. The measurement was done on *a. tibialis posterior* or *a. dorsalis pedis*, and the higher recorded value was recognized as the value of systolic pressure. For upper extremities, the measurement was done on *a. brachialis* (taking for ABI calculation the higher recorded value). ABI was calculated as the ratio of pressure in the pedal segments of tibial arteries to that in the brachial artery. Three measurements on each side were taken, calculating the average value for the left or right lower leg, and for the individual value, the lower obtained ABI value was taken. Based on the ABI, the examinees were divided into three categories: ABI≤0.9, ABI>0.9-<1.3, and ABI≥1.3.

4.3. Coronarography finding

The insight into the status of coronary circulation was made via the analysis of medical documentation, i.e. coronary angiography performed up to three months before the study. We analyzed the number of atherosclerotic changes in involved coronary arteries and percentage of stenosis in each of them.

4.4. Laboratory analysis

Standard laboratory techniques were used to measure glycemia and lipid status parameters (total cholesterol, HDL-C, LDL-C, triglycerids, and creatinine).

4.5. Anthropometric measurements

Anthropometric measurements (body weight, height, waist and hip circumference) were recorded in all examinees to gain information on their nourishment status. Body mass index (BMI) was calculated using the formula, weight(kg)/height(m^2). The waist/hip circumference ratio was also determined. Based on anamnesis and medical records, we analyzed the presence of changeable and unchangeable CV risk factors: hypertension, hyperlipidemia, smoking, diabetes, obesity, gender, and age.

4.6. Calculation of ten-year risk of fatal cardiovascular event using the SCORE system

An interactive electronic version of the SCORE risk charts, adjusted to high risk areas, were used to assess the risk of a fatal CV event.

4.6.1. Statistical processing

The description involved the following statistical parameters: arythmetic mean (Xsr), standard deviation (SD), minimum and maximum value of numerical descriptors, as well as the frequency and percentage (%) of attributive descriptors.

The comparison of mean values of numerical descriptors between the two groups of examinees was done using the Student's t-test or Mann-Whitney U-test in cases where the distribution of values did not conform to the normal distribution. The comparison of mean values of numerical descriptors between more than two groups of examinees was done using the analysis of variance (ANOVA) and Dunnet's *post hoc test.*

The frequency of attributive descriptors was assessed using the Mantel-Haenszel chi- square test or Fisher exact test when one of the expected frequencies was below five.

Linear regression analysis was used to assess the association of factors of interest. The values of regression coefficients (B) and their 95% confidence intervals were calculated. In multivariance models, only the factors demonstrating a significant impact on dependent variables in univariance analysis were included as independent variables. In addition to this method, multivariance analysis was done in the control of impact on dependent variables of age, gender, BMI, hyperlipoproteinemia, and diabetes, in which case these factors were retained as unconditional in the regression models, regardless of whether or not they had exerted significant effects upon dependent variables.

The results of statistical analysis were shown in tables and graphs. Quantitative statistical analysis was done on a PC. Calculations were accomplished using the SPSS program, 10.0 version.

5. Results

The study enrolled a total of 150 examinees and divided them into two groups. The first CP group consisted of patients with confirmed CAD and coronary angiography, confirming the presence of stenotic lesions (n=100). Most of them had some form of myocardial revascularization (47% surgically accomplished; 43% percutaneous coronary intervention). There were 7 patients with survived myocardial infarction without revascularization, and in 3 patients there was confirmed stable angina pectoris. Healthy examinees comprised the CG (n=50).

The examinees from the CP were 10 years older on average (59.74±10.45 vs 49.98±9.19 years; t=5.82; p<0.001), their CV risk score was three times higher (6.57±4.92 vs 1.76±1.3; z=7.66; p<0.001), and the average number of risk factors was more than twice as high compared to the control group (2.79±1.03 vs 0.98±0.71; z=8.48; p<0.001). The CP had mostly 3 (40.0%) and 2 (28.0%) manifest risk factors, where as controls had only one (50.0%) risk factor, and the difference in the distributions was statistically significant (χ^2=79.71; p<0.001).

5.1. Color Doppler sonography of the carotid arteries

The average CIMT in CP group examinees was statistically significantly higher (0.98±0.21 vs 0.67±0.12 mm; t=11.76; p<0.001), as well as the average number of plaques (2.11±1.50 vs 0.16±0.47; z=8.07; p<0.001) and percentage of stenosis (34.90±21.01 vs 3.44±9.53%; z=8.08; and p<0.001) than CG.

Out of 6 CG examinees with carotid plaques, fibrous plaques were observed in 5 (10.0%), and lipid plaques in one (2.0%) examinee. In the CP group, plaques were mostly fibrous too (50.0%), followed by fibrocalcified (22.0%) and calcified ones (10.0%).

5.2. Results of the ABI measurement

The average value in CG of ABI was 1.15±0.07 (range, 1.00-1.28), statistically significantly higher than in the CP group, where it was 1.02±0.21 on average (range, 0.71- 1.50) (t=5.62; p<0.001). In the CP group, 41.0% of patients had lower or normal ABI values and 18.0% had elevated values, while all controls had ABI values in the range of 0.91-1.29; the difference in these distributions was statistically (χ^2=48.63 and p<0.001).

5.3. Coronarography analysis

The average number of atherosclerosis involved coronary blood vessels was 2.22±0.81. All the patients from the CP group had atherosclerotic changes, 46.0% of which were observed in three blood vessels, 30.0% in two, and 24.0% in one vessel. Most of the patients (42%) had stenosis of over 70% in one blood vessel, 34% in two vessels, and 18% in three blood vessels, while only 6% was without stenosis of over 70% in any of their vessels.

The patients who had one blood vessel affected by atherosclerosis were statistically significantly younger than those with three affected vessels (53.88±10.68 vs 63.00±8.75 years; p<0.01), and their CV risk score (3.17±1.81) was significantly lower than that in patients with two (6.53±3.63; p<0.05) and three (8.37±5.80; p<0.001) involved blood vessels, as well as the average number of risk factors (2.29±1.00 vs 2.97±0.89 vs 2.93±1.06; and p<0.05). The patients with two affected blood vessels more commonly had four evident risk factors than those with one involved vessel, the difference being statistically significant (33.3% vs 8.3%; p<0.05). Only those with three affected blood vessels had five risk factors, which was observed in 4 (8.7%) examinees.

5.4. Analysis of the findings in carotid and coronary arteries

The patients with one coronary blood vessel affected by atherosclerosis had statistically significantly less fibrocalcified plaques (4.2 vs 32.6%; p<0.01) and a significantly lower average number of plaques (1.46±1.28 vs 2.46±1.53; p<0.05), compared to those with three involved blood vessels, and significantly less CIMT (0.86±0.20) compared to the patients with two (1.02±0.20; p<0.01) and three affected blood vessels (1.02±0.18; p<0.01) (Table 1).

5.5. ABI and coronarography finding

The value of ABI was lowest in the patients with three blood vessels affected by atherosclerosis (0.95±0.18) and statistically significantly lower than in those with only one affected blood vessel (1.12±0.20; p<0.01).

In patients with a single blood vessel affected by atherosclerosis, it was statistically more common to have normal (58.3%) and increased (29.2%) values of ABI compared to those with three affected blood vessels (32.6% and 8.7%) (p<0.05), and much more rarely lower ABI values (12.5%) compared to those with two (36.7%; p<0.05) and three (58.7%; p<0.001) affected blood vessels.

5.6. Association of the studied parameters with coronarography findings

The number of coronary blood vessels affected by atherosclerosis was significantly higher with CIMT, number of plaques, CV risk score, age, and waist-hip ratio increased by one unit of measurement: IMC thickness by 1.219; p<0.01; number of plaques by 0.141; p<0.01; CV risk score by 0.069; p<0.001; age by 0.027; p<0.001; and waist-hip ratio by 3.667; p<0.01. In patients with fibrocalcified plaques, the number of involved blood vessels was increased by 0.534; p<0.01. With each increase of ABI, valued by one unit of measurement, the number of involved blood vessels dropped by 1.298; p<0.01 (Table 2).

As the most important factors associated with the number of coronary blood vessels affected by atherosclerosis, multivariate regression analysis singled out ABI value, CIMT, fibrocalcified plaque type, CV risk score, and waist-hip ratio.

The number of coronary blood vessels affected by atherosclerosis was significantly higher with the increase of CIMT, CV risk score, and waist-hip ratio by one measurement unit: CIMT by 0.729; p<0.05; CV risk score by 0.033; p<0.05; and waist-hip ratio by 3.182; p<0.01. With each increase of ABI value by one measurement unit, the number of involved blood vessels dropped by 0.844; p<0.05 (Table 3).

When the multivariate regression analysis also involved the control of effects of age, gender, hyperlipoproteinemia, and diabetes, the most significant factors associated with the number of coronary blood vessels affected by atherosclerosis were ABI values and waist-hip ratio.

Table 1. Comparison of Doppler characteristics in the carotids of the affected related to the numberof affected coronary blood vesels

Characteristic	No of affected blood vessels: One (n=24)	Two (n=30)	Three (n=46)	Comparison (p value)
CIMT(mm)	0.86±0.20	1.02±0.20	1.02±0.18	I vs II: p=0.006 I vs III: p=0.002
Percentage of stenosis	27.33±18.23	36.80±24.68	37.61±19.20	n.s.
Plaque properties				
No plaques	6 (25.0%)	6 (20.0%)	4 (8.7%)	n.s.
Fibrous	14 (58.3%)	14 (46.7%)	22 (47.8%)	n.s.
Calcified	3 (12.5%)	4 (13.3%)	3 (6.5%)	n.s.
Fibrocalcified	1 (4.2%)	6 (20.0%)	15 (32.6%)	I vs III: p=0.007
Fibrolipid	-	-	2 (4.3%)	n.s.
Average number of plaques	1.46±1.28	2.10±1.49	2.46±1,53	I vs III: p=0.022

CIMT – carotid intima-media thickness

Table 2. Evaluation of the association of risk factors of interest with the number of afftected coronary blood vessels: univariate regression analysis

Factor	B	SE	r	t	p	Limits of 95% CI for B	
						Upper	Lower
ABI	-1.298	0.363	-0.340	3.58	**0.001**	-2.019	-0.578
CIMT (mm)	1.219	0.389	0.301	3.13	**0.002**	0.446	1.991
Percentage of stenosis of the carotids	0.007	0.004	0.181	1.83	0.071	-0.001	0.015
No of plaques	0.141	0.053	0.262	2.68	**0.009**	0.037	0.246
Plaque properties							
No plaques	-0.411	0.219	-0.187	1..88	0.063	-0.844	0.023
Fibrous	-0.120	0.163	-0.074	0.74	0.462	-0.443	0.203
Calcified	-0.244	0.271	-0.091	0.90	0.369	-0.782	0.293
Fibrocalcified	0.534	0.189	0.274	2.82	**0.006**	0.158	0.909
Fibrolipid	0.796	0.577	0.138	1.38	0.171	-0.349	1.941
CV risk score	0.069	0.015	0.416	4.53	**<0.001**	0.039	0.099
Female gender	-0.319	0.161	-0.197	1.99	**0.050**	-0.638	0.000
Age (years)	0.027	0.007	0.346	3.65	**<0.001**	0.012	0.041
BMI (kg/m^2)	-0.005	0.020	-0.027	0.27	0.791	-0.045	0.034
Waist circumference (cm)	0.009	0.007	0.119	1.19	0.238	-0.006	0.023
Waist-hip ratio	3.667	1.046	0.334	3.50	**0.001**	1.590	5.744
Diabetes	0.385	0.196	0.194	1.96	0.053	-0.005	0.774

ABI – ankle-brachial index; CIMT – carotid intima-media thickness; BMI – body mass index

Table 3. Evaluation of the association of investigated parameters and the number of affected coronary blood vessels: results of mutivariate regression analysis

Factor	B	SE	r	t	p	Limits of 95% CI for B	
						Upper	Upper
ABI	- 0,844	0,339	- 0,221	2,50	**0,014**	-1,516	-0,172
CIMT (mm)	0,729	0,351	0,180	2,08	**0,040**	0,033	1,426
Fibrocalcified plaque type	0,295	0,174	0,152	1,70	0,092	-0,050	0,640
CV risk score	0,033	0,016	0,203	2,16	**0,033**	0,003	0,064
Waist-hip ratio	3,182	0,941	0,290	3,38	**0,001**	1,313	5,051
Regression constant	- 0,890	0,980		0,91	0,366	-2,836	1,056

ABI – ankle-brachial index; CIMT – carotid intima-media thickness;.

The number of coronary blood vessels affected by atherosclerosis was significantly higher with the increase of waist-hip ratio by 2.913; $p<0.01$. With each increase of ABI value by one measurement unit, the number of involved blood vessels dropped by 0.823; $p<0.05$ (Table 4).

6. Discussion

More than a third of coronary events occur in individuals without a previous history of anginal pain. More importnatly, a sixth of clinical events occur in patients with stenoses of over 70% in the coronary arteries, and a huge majority in cases with „hemodynamically insignificant" lesions that cannot be detected with traditional methods (stress tests and angiography). This would

Table 4. Evaluation of the association of investigated parameters and the number of affected coronary blood vessels with the control for impacts of age, gender, hyperlipoproteinemia, and diabetes

Factor	B	SE	r	t	p	Limits of 95% CI for B	
						Upper	Upper
ABI	- 0.823	0.339	- 0.215	2.43	**0.017**	- 1.497	-0.149
CIMT (mm)	0.670	0.366	0.166	1.83	0.071	- 0.058	1.397
Fibrocalcified plaque type	0.230	0.182	0.118	1.27	0.208	- 0.131	0.592
CV risk score	0.021	0.020	0.130	1.09	0.278	- 0.017	0.060
Waist-hip ratio	2.913	0.966	0.265	3.02	**0.003**	0.994	4.832
Age (years)	0.008	0.009	0.097	0.82	0.413	- 0.011	0.026
Gender	- 0.194	0.163	- 0.119	1.19	0.238	- 0.517	0.130
Hyperlipoproteinemia	0.115	0.198	0.050	0.58	0.562	- 0.278	0.509
Diabetes	0.276	0.166	0.139	1.66	0.100	-0.054	0.607
Regression constant	- 1.027	1.073		0.96	0.341	- 3.159	1.105

ABI – ankle-brachial index; CIMT – carotid intima-media thickness;.

indicate the need for the detection of subclinical atherosclerosis, much before it becomes clinically significant and evident, especially because nowadays there are therapeutic options that can stop or even reverse the process of coronary atherosclerosis [5].

Our study aimed to analyze the significance of simple widely available methods, such as ABI determination and color Doppler sonography of the magistral blood vessels in the neck. In the most recent guidelines for the treatment and diagnosis of hypertension, these methods have been described as simple, widely available to a broad spectrum of people, relatively cheap, with a good predictive ability [6]. Moreover, the latest recommendations of the American College of Cardiology and American Heart Association have referred to these methods as appropriate in the screening of asymptomatic individuals with a moderate-medium risk of cardiovascular disease [7].

The ABI is the simplest indicator of atherosclerotic changes in the arteries of the lower extremities, representing the basic non-invasive method in the diagnosis of peripheral occlusive disease and surveillance after revascularization procedures [8,9]. In addition to the role in confirming PAD, a low ABI is a good predictor of adverse cardiovascular events and mortality [10]. In our examinees, patients with CAD, the average value of ABI was 1.02, ranging from 0.75-1.50, which is statistically significantly lower than in control examinees.

One of the basic questions to be elucidated in our study was a possible association of ABI with coronary disease in our subjects. The results demonstrated that there was a significant association of ABI with coronary blood vessel changes. The association increased with the number of affected coronary blood vessels. The patients with two-vessel and three-vessel coronary disease had, on average, lower ABI values compared to those with one-vessel coronary disease. This significant correlation persisted even after mutivariance analysis with other risk factors and investigated parameters. Our results corroborate the results of Papamichael CM et al., who demonstrated the association of ABI with the severity of coronary disease, determined via the number of affected coronary blood vessels ($p<0.04$) and Gensini angiography score ($p<0.01$) [11]. Similar to this, Nunez et al. reported that the value of ABI≤0.9 in patients with acute coronary syndrome was a good predictor of multivessel coronary disease [12]. The PAMISCA study showed that the patients with acute coronary syndrome and ABI≤0.9 were exposed to greater risks of cardiac death and coronary disease complications (angina pectoris, heart failure, and atrial fibrillation) [13].

These results may explain the parallel process of development of atherosclerosis in the coronary and peripheral blood vessels. Single vessel coronary disease is mostly associated with a short history of angina pectoris, and it is most commonly the cause of acute coronary syndrome, associated in this case with the rupture of soft tissue „young" plaques. All this is related more to the acute form of coronary disease than to the duration of atherosclerosis. A lower value of ABI would rather suggest generalized atherosclerosis, a long term process of atherosclerosis, and the development of multivessel coronary disease. The drop of ABI<0.15 in three years increases the risk of overall mortality (RR: 2.4) and CV mortality (RR: 2.9) [14]. These results suggest the need for more serious treatment of risk factors in asymptomatic individuals with a low ABI.

The CIMT of the common carotid arteries is a good indicator of early atherosclerosis. Literature data demonstrates a clear association between CV risk factors and IMC thickness, in a similar way as between CIMT and clinical manifestations of coronary disease [2,15,16]. In the ARIC study, with 13.145 examinees followed up for 15 years, use of the CIMT and carotid plaque(s) together with traditional risk factors in patients with moderate risk level (10-20% ten-year risk) improved the accuracy by 9.9% in the assessment of risk of severe coronary events and revascularization [17].

The mean time required to perform the scans on the outpatient department was 7.3 min (range 4.5 to 16.7 min). A high level of accuracy for detecting plaques (sensitivity 78.5%; specificity 93.6%) was achieved. Identifying abnormal IMT had lower sensitivity but adequate specificity of 46.7% and 87.6%, respectively [18].

Average CIMT in our patients was 0.98 mm, significantly more than in healthy individuals. Our patients with two and three-vessel coronary disease had significantly thicker CIM compared to those with single vessel disease. In addition to CIMT measurements, our study aimed to analyze the presence of plaques in the carotid arteries, the degree of stenosis produced, and especially to analyze plaque properties and quality. The average number of plaques in our patients was 2.11, and the percentage of stenosis, 34.9%, was markedly higher than in the control group. Similar results were reported by Khoury et al., showing that the patients with multivessel coronary disease had a higher carotid plaque score compared to those with single vessel coronary disease or normal coronary vessels ($p<0.001$) [19].

7. Conclusion

Our results demonstrated a significant association of pathologic changes in the peripheral with those in coronary blood vessels. It was shown that reduced ABI values and CIMT were in correlation with the severity of coronary disease assessed based on the number of affected coronary blood vessels and degree of stenosis of the confirmed lesions.

This can be useful in the assessment of CV risk and selection of appropriate therapy, since the patients with pathologic findings require a more aggressive treatment of changeable risk factors and more intensive therapy involving blood pressure control, use of statins, and antiaggregation therapy.

Acknowledgements

This work was supported by a grant No 175092, from The Ministry of Science and Technological Development of Serbia.

Conflict of interest

Not declared.

References

[1] 011ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/ SVS Guideline on the Management of Patients With Extracranial Carotid and Vertebral Artery Disease. J Am Coll Cardiol 2011; 57 (8): 1002–1044

[2] Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation 2007; 115(4): 459-467

[3] Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 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). J Am Coll Cardiol 2006; 47: e1–e192

[4] Fowkes FGR, 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. JAMA 2008; 300(2): 197–208

[5] Little WC, Constantinescu M, Applegate RJ, Kutcher MA, Burrows MT, Kahl FR, et al. Can coronary angiography predict the site of a subsequent

myocardial infarction in patients with mild –to-moderate coronary diemeter? Circulation 1988; 78: 1157–1166
[6] Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. Journal of Hypertension 2009; 27 (11): 2121–2158
[7] 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010; 56: e50–e103
[8] 2011 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Peripheral Artery Disease (Updating the 2005 Guideline). A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011; 124 (18): 2020–2045
[9] Olin JW, Allie DE, Belkin M, Bonow RO, Casey DE Jr, Creager MA, et al. ACCF/AHA/ACR/SCAI/SIR/SVM/SVN/SVS 2010 Performance Measures for Adults With Peripheral Artery Disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Performance Measures, the American College of Radiology, the Society for Cardiac Angiography and Interventions, the Society for Interventional Radiology, the Society for Vascular Medicine, the Society for Vascular Nursing, and the Society for Vascular Surgery (Writing Committee to Develop Clinical Performance Measures for Peripheral Artery Disease). J Am Coll Cardiol 2010; 56: 2147–2181
[10] Tendera M, Aboyans V, Bartelink ML, Baumgartner I, Clément D, Collet JP, et al. ESC Guidelines on the diagnosis and treatment of peripheral artery diseases. Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries. The Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J 2011; 32(22): 2851–2906
[11] Papamichael CM, Lekakis JP, Stamatelopoulos KS, Papaioannou TG, Alevizaki MK, Cimponeriu AT, et al. Ankle-Brachial Index as a Predictor of the Extent of Coronary Atherosclerosis and Cardiovascular Events in Patients With Coronary Artery Disease. Am J Cardiol 2000; 86: 615–618
[12] Nunez D, Morillas P, Quiles J, Cordero A, Guindo J, Soria F, et al. a on behalf of the PAMISCA study researchers. Usefulness of an Abnormal Ankle-Brachial Index for Detecting Multivessel Coronary Disease in Patients With Acute Coronary Syndrome. Rev Esp Cardiol 2010; 63(1): 54–59
[13] Bertomeu V, Morillas P, Gonzalez-Juanatey JR, Quiles J,Guindo J, Soria F, et al. Prevalence and prognostic influence of peripheral arterial disease in patients >or=40 years old admitted into hospital following an acute coronary event. Eur J Vasc Endovasc Surg 2008; 36:189–196
[14] Criqui MH, Ninomiya 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): 1736–174
[15] Mannami T, Baba S, Ogata J. Strong and significant relationships between aggregation of major coronary risk factors and the acceleration of carotid atherosclerosis in the general population of a Japanese city. Arch Intern Med 2000; 160: 2297–2303
[16] Nguyen-Thanh HT, Benzaquen BS. Screening for subclinical coronary artery disease measuring carotid intima media thickness. Am J Cardiol. 2009; 104(10): 1383–1388
[17] Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, et al. Carotid intima- media thickness and the presence or absence of plaque improves prediction of coronary heart disease risk in the Atherosclerosis Risk in Communities (ARIC) study. J Am Coll Cardiol 2010; 55: 1600–1607
[18] Ray A, Tamsma JT, Hovens MM, op ‘t Roodt J, Huisman MV. Accuracy of carotid plaque detection and intima-media thickness measurement with ultrasonography in routine clinical practice. Eur J Intern Med. 2010 Feb; 21(1): 35–39
[19] Khoury Z, Schwartz R, Gottlieb S, Chenzbraun A, Stern S and Keren A. Relation of Coronary Artery Disease to Atherosclerotic Disease in the Aorta, Carotid, and Femoral Arteries Evaluated by Ultrasound. Am J Cardiol 1997; 80: 1429–1433