UNIVERSA MEDICINA

May-August, 2016 *Vol.35 - No.2*

High blood pressure tends to increase carotid intima-media thickness in adult females

Yudhisman Imran*, Pukovisa Prawiroharjo, and Martiem Mawi*****

ABSTRACT

BACKGROUND
Atherosclerosis is initiated by endothelial dysfunction, as a result of increasing degradation of nitrit oxide by reactive oxygen species, thereby increasing oxydative stress. Dyslipidemia is one of the risk factors of endothelial dysfunction. The aim of this study was to evaluate the relationship of blood pressure and serum lipid level with carotid intima-media thickness (CIMT) in subjects aged between 55-65 years.

METHODS
A cross sectional study was carried out in 52 male and female subjects aged between 55-65 years. Age, gender, body mass index (BMI), blood pressure, lipid profile, and CIMT were assessed in all subjects. The independent t-test was used to to analyze the relationship between all variables and CIMT. The level of statistical significance was set at $p<0.05$

RESULTS
Mean age was 59.19 ± 3.68 years, prevalence of thickened CIMT was 66.5%, and plaques were found in 9 subjects. There were no significant differences in age, BMI, systolic and diastolic blood pressure, and lipid profile between normal and thickened CIMT ($p>0.05$). However, there was a significant difference in gender between the two groups ($p=0.011$). In females, mean systolic and diastolic blood pressure were higher in the thickened CIMT group than in the normal CIMT group, but the difference was not significant ($p>0.05$).

CONCLUSIONS
Our findings suggest that high blood pressure tends to increase CIMT in female adults. An increasing value of CIMT should be considered as a sign of cerebrovascular disease.

Keywords: Atherosclerosis, blood pressure, lipid, carotid intima-media thickness, adult

*Department of Neurology,
Faculty of Medicine,
Trisakti University, Jakarta
**Department of Neurology,
Cipto Mangunkusumo General Hospital, Faculty of Medicine,
University of Indonesia, Jakarta
***Department of Physiology,
Faculty of Medicine,
Trisakti University, Jakarta

Correspondence :
dr. Yudhisman Imran, Sp.S
Department of Neurology
Faculty of Medicine
Trisakti University
Jl. Kyai Tapa No. 260 – Grogol
Jakarta 11440
Phone : +62813 1945 9868
Email:
yudhisman.imran@trisakti.ac.id

Univ Med 2016;35:135-42
DOI: http://dx.doi.org/10.1805/UnivMed.2016.v35.135-142

INTRODUCTION

The increased longivity of the population is reflected in the high numbers of the elderly in the population. In Indonesia in the year 2010, there were 18,037,009 elderly or around 7.59% of the population, and their number is projected to increase to 414% between the years 1990 and 2025.[1] The age of an individual advances with increasing oxidative stress of protein and lipid biomolecules. This increased oxidative stress will raise the risk of vascular diseases such heart disease and stroke, thus causing a decreased quality of life of the elderly.[2] The data in Indonesia show a rising trend of stroke cases, with regard to mortality, morbidity, or disability. The age-related mortality rates are 15.9% (age group of 45-55 years), 26.8% (age group of 55-64 years) and 23.5% (age group of >65 years).[3] Atherosclerosis, one of the causative factors of ischemic stroke, is a chronic inflammatory process, which leads to the formation of the initial lesion. This lesion develops into a more complex one and may even cause an acute lesion such as a ruptured plaque. Atherosclerosis commences with endothelial dysfunction in the form of thickening of the intima media complex (IMC). The endothelial dysfunction is the result of decreased bioavailability of nitric oxide (NO), which is known as a vasodilator resulting from increased NO degradation by reactive oxygen species (ROS). Free radicals are produced continuously in the body for physiological purposes. If they are present in excessive amounts, they will cause a pathological condition known as oxidative stress.[4,5]

In dyslipidemia there is an increase in the blood cholesterol concentration. Total cholesterol may be categorized into several diagnostic lipoprotein profiles, comprising high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, intermediate density lipoprotein (IDL) cholesterol and very low density lipoprotein (VLDL) cholesterol, chylomicrons remnants, and triglycerides. The optimal total cholesterol concentration is <200 mg/dL, that of LDL cholesterol <100 mg/dL, HDL cholesterol >40 mg/dL, and triglycerides <150 mg/dL.[6,7]

The high LDL cholesterol concentration in the circulation and the decrease in the concentration of HDL cholesterol, which serves to transport cholesterol from the tissues to the liver, play a role in atherosclerosis. Subsequently LDL cholesterol adheres to the damaged endothelium and undergoes oxidative modification in the subendothelial space into oxidized LDL cholesterol (ox LDL), which has proinflammatory activity but may still be recognized by LDL receptors. Initially, the endothelium attempts to repair itself by attracting T lymphocytes, monocytes and platelets to the site of injury. When the repair process fails, the endothelium becomes more permeable and the lymphocytes and monocytes migrate to the subendothelial space by a process of adhesion. The monocytes develop into macrophages and express scavenger receptors, thus forming foam cells. The abovementioned oxidative modification comprises reactive oxygen species (ROS) produced by endothelial cells and macrophages. The increase in ROS leads to decreased nitric oxide (NO) production and bioavailability, resulting in vasoconstriction and platelet aggregation.[5,8]

An increase in carotid intima-media thickness (CIMT) can be detected by noninvasive ultrasound (USG) techniques. The USG examination can evaluate the vessel wall structure, which has a characteristic double reflection with an intermediate hyperechoic zone, designated the intima media complex (IMC), and used as a parameter of atherosclerosis. The IMC value increases with advancing age. The normal IMC value is <0.8mm for Asian populations, and a thickening of 1mm is considered abnormal and is suspected as a lesion of lipid disorders.[9,10]

One study investigating the association between cholesterol concentration and IMC thickness was conducted by Enomoto et al.[11] showing a significant association between HDL cholesterol and IMC. Differing results were

shown by Yang et al.[12] who found no significant association between mean IMC and mean HDL cholesterol. These inconsistent study results call for futher research. Therefore, the purpose of the present study was to differentiate serum lipid concentrations and carotid intima-media thickness (CIMT) in males and females aged between 55-65 years.

METHODS

Research design

This was an analytical study of cross-sectional design, conducted at the Puskesmas of Mampang Prapatan district, South Jakarta, from August 2013 until February 2014.

Study subjects

The subjects of this study were elderly residents of Mampang Prapatan district, South Jakarta, aged between 55-65 years, who were selected randomly. The inclusion criteria in this study were age between 55-65 years, agreeing to participate in this study, capable of active locomotion without walking aids, capable of answering the questions of the investigator on her/his own or with the aid of other persons. The exclusion criteria were a history of hypertension, diabetes mellitus, heart disease, stroke, smoking, consumption of cholesterol-lowering drugs and incomplete participation in the study. A total of 177 respondents were interviewed by 8 interviewers (Puskesmas cadres) using a questionnaire. Then physical examinations and measurements of serum lipid concentration were performed. Of the 177 respondents who had a laboratory examination there were 70 respondents who fulfilled the inclusion criteria. However, only 52 subjects agreed to undergo doppler ultrasound (USG) examination.

Measurement of carotid intima-media thickness

The protocol for CIMT measurement has been published elsewhere.[13] Carotid duplex USG was performed, in which the subjects were lying supine with the neck slighly extended and rotated away from the side to be examined. The 10 MHz linear transducer was placed on the neck and moved upwards from the supraclavicular region to the right and left mandibular angles. The measurement was performed on the distal part of the common carotid artery, i.e. on a 1-cm long segment of the carotid bulb. On the screen a double-line would be visible, indicating the simultaneous capture of the near-wall and the far-wall. The CIMT measurement results were reported in millimeters (mm). The instrument used was the Mindray Z6 Digital Ultrasonic Imaging system. The CIMT examination was performed on 52 subjects at the Mampang Prapatan district Puskesmas.

The laboratory examinations were performed in the Prodia clinical laboratory, while the carotid doppler examination was carried out by the investigators. The CIMT results were divided into two categories: normal if CIMT was <0.8 mm and thickened if CIMT was ≥0.8 mm.[14]

Measurement of body mass index

Height was measured by means of a portable microtoise and expressed in cm with a precision of 0.1 cm, weight was measured using Sage portable scales and expressed in kg with a precision of 0.1 kg. Body mass index (BMI) was calculated from the weight in kg divided by height in meters squared and divided into the following categories: underweight (<18.5 kg/m^2), normal (18.5-22.9 kg/m^2), overweight (23.0-27.5 kg/m^2) and obesity (>27 kg/m^2). Blood pressure measurement results were expressed in mmHg.

Measurement serum lipid concentrations

A 10-mL blood sample was collected by venipuncture from the cubital vein of each subject, after an overnight fast of 12-14 hours, then the blood sample was centrifuged at 3000 rpm for 15 minutes. The serum was separated and placed in an automatic analyzer. Serum lipids were determined directly in the Prodia laboratory at each laboratory examination. The

normal total cholesterol concentration was defined at <200mg/dL, LDL cholesterol <100mg/dL, HDL >40mg/dL, and triglycerides <150mg/dL. Determination of cholesterol concentration was performed by the CHOD-PAP method, with a coefficient of variation of 1.19 and April 2016 as expiration date. For LDL and HDL cholesterol determinations, the coefficient of variations were 1.43 and 2, respectively, with expiration date 2 February 2016. Triglycerides were measured by the GDHNAD method, with a coefficient of variation of 1.27. Glucose was determined by the GODPAP method, with coefficient of variation 1.05 and expiration date 1 January 2017.

Statistical analysis

The comparison of lipid variables and CIMT was done with the independent- t test. The level of statistical significance was set at $p<0.05$.

Ethical clearance

This study was given ethical clearance by the Ethics Commision, Faculty of Medicine, Trisakti University (No. 55/KER/FK/05/2013).

RESULTS

The 52 subjects had a mean age of 59.19 ± 3.68 years and 28 (53.8%) were females, while 40.4% had finished primary school and 80.8% was unemployed. Based on the results of body mass index measurements the mean BMI was 24.55 ± 3.42 kg/m^2. Mean systolic blood pressure was 138.17 ± 21.78 mmHg and mean diastolic blood pressure 83.07 ± 9.90 mmHg. A total of 45 (66.5%) subjects had thickened CIMT (Table 1). On lipid profile examination the mean total cholesterol (TC) concentration was 202.19 ± 35.66 mg/dL, mean LDL cholesterol 138.34 ± 32.36 mg/dL, mean HDL cholesterol 47.34 ± 8.53 mg/dL, and mean triglyceride (TG) concentration was 135.09 ± 66.03 mg/dL (Table 1). There were plaques in 9 subjects with mean age of 60.05 ± 3.97 years.

In comparison with the normal CIMT group, the parameters of age, body mass index, systolic blood pressure and levels of TC, TG and LDL in the group with thickened CIMT did not show statistically significant differences ($p>0.05$). However, of the male subjects 24 (100.0%) had thickened CIMT, thus differing significantly from the females, of whom 21 (75.0%) had thickened CIMT ($p=0.011$) (Table 2).

The results of the analysis show a difference in gender between both CIMT groups. Stratification analysis of the females showed thickened CIMT, while the systolic (143.33 ± 22.66 mmHg) and diastolic blood pressures (86.43 ± 8.68) tended to be higher in comparison with the normal CIMT group, although the difference was statistically not significant ($p>0.05$) (Table 3.)

Table 1. Distribution of subjects by characteristics and biochemical indicators (n=52)

Characteristic	n (%)
Age (years)	59.19 ± 3.67
Gender	
Female	30 (57.7)
Male	22 (42.3)
Education	
Primary school	21 (40.4)
Junior high school	13 (25)
Senior high school	15 (28.8)
Academy	3 (5.8)
Employment status	
Employed	10 (19.2)
Unemployed	42 (80.8)
CIMT	
Normal	7 (13.5)
Thickened	45 (66.5)
Body mass index (kg/m^2)	24.55 ± 3.32
Systolic BP (mmHg)	138.17 ± 21.78
Diastolic BP (mmHg)	83.07 ± 9.90
Total cholesterol (mg/dL)	202.19 ± 35.66
LDL cholesterol (mg/dL)	138.34 ± 32.36
HDL cholesterol (mg/dL)	47.34 ± 8.53
Triglycerides (mg/dL)	135.09 ± 66.03

CIMT: carotid intima media thickness; BP: blood pressure; LDL: low density lipoprotein; HDL: high density lipoprotein

DISCUSSION

Our study results show a significantly greater CIMT prevalence in males than in females.

Table 2. Comparison between normal CIMT group and thickened CIMT group in terms of general information and biochemical indicators

Characteristic	Normal CIMT (n=7)	Thickened CIMT (n=45)	p
Age (years)	57.43 ± 3.05	59.47 ± 3.72	0.175
Gender			0.011*
Female (n(%)	7 (25.0)	21 (75.0)	
Male (n,%)	0 (0.0)	24 (100.0)	
Systolic BP (mmHg)	127.86 ± 19.55	139.78 ± 21.87	0.381
Diastolic BP (mmHg)	78.57 ± 10.69	83.78 ± 9.72	0.199
Body mass index (kg/m^2)	27.06 ± 3.72	24.16 ± 3.25	0.381
Total cholesterol (mg/dL)	203.43 ± 30.98	202.00 ± 36.63	0.923
LDL cholesterol (mg/dL)	141.57 ± 28.48	137.84 ± 33.19	0.780
HDL cholesterol (mg/dL)	45.86 ± 7.67	47.58 ± 8.72	0.625
Triglycerides (mg/dL)	150.29 ± 65.81	132.73 ± 66.49	0.518

CIMT: carotid intima media thickness; BP: blood pressure; LDL: low density lipoprotein; HDL: high density lipoprotein

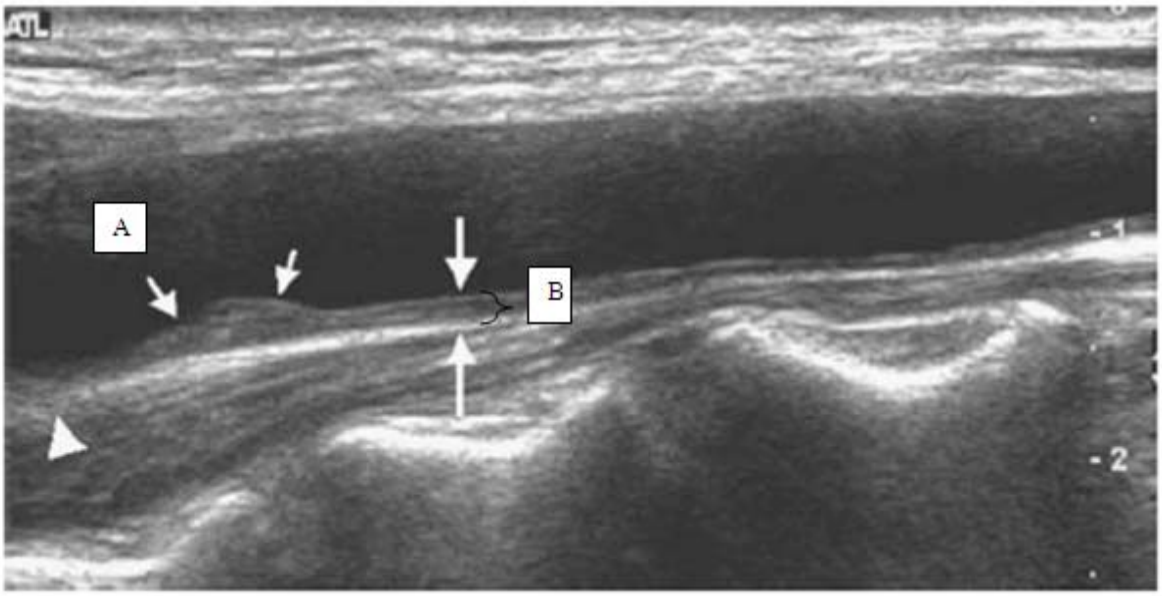
Differing results were shown in the study of Guan et al.[15] where the prevalence of thickened CIMT was significantly higher than in females. In our study, mean systolic blood pressure (SBP) and mean diastolic blood pressure (DBP) were higher in the thickened CIMT group compared with the normal CIMT group, but the difference was statistically not significant. Different results were obtained in the study by Guan et al.[15] showing that SBP was significantly higher in the thickened CIMT group compared with the normal CIMT group, but that DBP was not significantly different. Another study showed different results, in that both systolic and diastolic BP were found to be positively associated with CIMT.[16] High BP has been recognized as an important risk factor for cardiovascular and cerebrovascular diseases. Although high BP is a major determinant of CIMT, the associations between CIMT and different types of abnormal BP in different populations remain unknown. In an investigation enrolling 129 subjects aged from 29 to 94 years, a positive association was shown between aging and CIMT. In relation to systolic hypertension, a significant association was observed with CIMT.[18]

As a result of the systemic diffuse lesions of atherosclerosis, vital organs such as the heart, brain and kidney may undergo structural and functional alterations.[19] The diagnosis of subclinical atherosclerosis can be based on CIMT measurement by ultrasonography, which may facilitate its assessment and early intervention. Atherosclerosis is currently viewed as a multi-factorial disease, where the most important pathogenic factors are lipid metabolic disorders, which play an important role in its development.[20] In atherosclerosis, endothelial dysfunction occurs

Table 3. Comparison between females of the normal and thickened CIMT groups in terms of general information and biochemical indicators (n=28)

Characteristic	Normal CIMT (n=7)	Thickened CIMT (n=21)	p
Age (years)	57.43 ± 3.05	59.86 ± 3.62	0.124
Systolic BP (mmHg)	127.86 ± 19.55	143.33 ± 22.66	0.119
Diastolic BP (mmHg)	78.57 ± 10.69	86.43 ± 8.68	0.061
Body mass index (kg/m^2)	27.06 ± 3.72	24.45 ± 3.32	0.094
Total cholesterol (mg/dL)	203.43 ± 30.98	207.67 ± 34.79	0.776
LDL cholesterol (mg/dL)	141.57 ± 28.48	141.38 ± 33.38	0.989
HDL cholesterol (mg/dL)	45.86 ± 7.67	49.28 ± 7.96	0.325
Triglycerides (mg/dL)	150.29 ± 65.81	133.52 ± 51.67	0.493

CIMT: carotid intima media thickness; BP: blood pressure; LDL: low density lipoprotein; HDL: high density lipoprotein



Legend: A: Plaque; B: IMC
Figure 1. Intima-media complex (IMC)[9]

as a result of chronic inflammation, which includes decreased nitrite oxide (NO) production, increased expression of prothrombotic factors, proinflammatory adhesion molecules, cytokines, and chemotactic factors, in addition to increased reactive oxygen species (ROS). Low NO bioavailability increases the expression of several adhesion molecules, such as vascular cell adhesion molecule-1 (VCAM-1), intracellular adhesion molecule-1 (ICAM-1), platelet endothelial adhesion molecule-1 (PECAM-1), and integrins and selectins. Furthermore, these adhesion molecules induce recruitment and adhesion of monocytes, T lymphocytes, and thrombocytes on the endothelium.[21,22] Thickening of IMC is also increased by various proinflammatory mediators and other types of oxidative stress.

Based on the obtained results, the limitations in this study were that no assessment was done on physical activity, dietary pattern, socio-demographic characteristics of the subjects, and on other oxidative biomarkers. The study method used was cross-sectional, so that no control was possible for confounding factors, other than those capable of causing bias.

Although the association of CIMT and increased risk of cardiovascular events is an established fact, there is still insufficient evidence to indicate that decreased CIMT will lead to a reduction in CVD. In addition, subclinical atherosclerosis is mostly considered a non-causal and nonspecific marker of atherosclerotic complications.[23] The use of standardized methods in CIMT measurement is required for further investigations, since CIMT reflects atherosclerosis in its initial stages. Carotid plaque area may be a better measure of atherosclerosis than CIMT or plaque thickness, since on average plaque area possibly increases at twice its rate of thickening.[24]

It is recommended to conduct further studies of cohort design, with larger sample sizes and broader age ranges. The benefits will better felt if other biomarkers of oxidative stress are also evaluated.

CONCLUSIONS

Our study found that high blood pressure tends to increase CIMT thickening in adult females. On persons with high blood pressure and increased total and LDL cholesterol, regular health checks should be performed, especially carotid ultrasound examination, for early identification and prevention, and delayed development of atherosclerosis.

CONFLICT OF INTERESTS

None declared.

ACKNOWLEDGEMENTS

The investigators thank the Dean and Vice-Deans of the Faculty of Medicine, Trisakti University, for moral and material support in the conduct of this study. Thanks are also due to the Head of Mampang Health center (Puskesmas Mampang) and staff, and to the study participants.

REFERENCES

1. Badan Perencanaan Pembangunan Nasional, Badan Pusat Statistik, United Nations Population Funds. Proyeksi penduduk Indonesia 2010-2035. Jakarta: Badan Pusat Statistik;2013.
2. Dawis NE. Atherosclerosis an inflammatory process. J Insur Med 2005;37:72-5.
3. Pokdi Stroke Perhimpunan Dokter Spesialis Saraf Indonesia (PERDOSSI) Guideline stroke tahun 2011. Jakarta: Perhimpunan Dokter Spesialis Saraf Indonesia (PERDOSSI); 2011.
4. Vogiatzi G, Tousoulis D, Stefanadis C. The role of oxidative stress in atherosclerosis. Hellenic J Cardiol 2009;50:402- 9.
5. Kaur J, Arora S, Singh B, et al. Role of oxidative stress in pathophysiology of transient ischemic attack and stroke. Int J Biol Med Res 2011;2:611-5.
6. Jelllingen PS, Smith DA, Metha AE, et al. American association of clinical endocrinologists guidelines for management of dyslipidemia and prevention of atherosclerosis. Endocr Pract 2012; 18:1-78.
7. Stapleton PA, Goodwill AG, James ME, et al. Hypercholesterolemia and microvascular dysfunction interventional strategies. J Inflamm 2010;7:1-10.
8. Saba L, Sanfilippo R, Montisci R, et al. Assosiations between carotid artery wall thickness and cardiovascular risk factors using multidetector CT. Am J Neuroradiol 2010;31: 1758-63.
9. Hurst RT, Ng DW, Kendall C, et al. Clinical use of carotid intima-media thickness: review of the literature. J Am Soc Echocardiogr 2007;20:907-14.
10. Schaberle W. Ultrasonography in vascular diagnosis: a therapy-oriented textbook and atlas. Berlin: Springer Verlag;2011.
11. Enomoto M, Adachi H, Hirai Y, et al. LDL-C/ HDL-C ratio predicts carotid intima-media thickness progression than HDL-C or LDL-C alone. J Lipid 201.Article ID 549137, 6 pages. http://dx.doi.org/10.1155/2011/549137.
12. Yang C, Sun Z, Li Y, et al. The correlation between serum lipid profile with carotid intima-media thickness and plaque. BMC Cardiovasc Disord 2014;14:81-91.
13. Liang LR, Wong ND, Shi P, et al. Cross-sectional and longitudinal association of cigarette smoking with carotid atherosclerosis in Chinese adults. Prev Med 2009;49:62–7.
14. Liviakis L, Pogue B, Paramsothy P, et al. Carotid intima-media thickness for the practicing lipidologist. J Clin Lipidol 2010;4:24–35.
15. Guan YY, Li M, Chen XO, et al. Association between blood lipid levels and carotid intima-media thickness in Shanghai urban population. J Transl Intern Med 2013;1:36-9.
16. Ayer JG, Harmer JA, Nakhla S, et al. HDL cholesterol, blood pressure, and asymmetric dimethylarginine are significantly associated with arterial wall thickness in children. Arterioscler Thromb Vasc Biol 2009;29:943-9.
17. Acevedo M, Kramer V, Tagle R, et al. Cardiovascular risk factors among young subjects with high carotid intima media thickness. Rev Med Chil 2011;139:1322-9.
18. Viana de Freitas E, Brandão AA, Pozzan A, et al. Study of the intima-media thickening in carotid arteries of healthy elderly with high blood pressure and elderly with high blood pressure and dyslipidemia. Clin Intervent Aging 2008;3: 525–34.
19. Uno K, Nicholls SJ. Biomarkers of inflammation and oxidative stress in atherosclerosis. Biomark Med 2010;4:361-73.
20. Morrison KM, Dyal L, Conner W, et al. Cardiovascular risk factors and non-invasive assessment of subclinical atherosclerosis in youth. Atherosclerosis 2010;208:501-5.
21. Sengupta D, Bardhan J, Mahapatra AB, et al. Corelation between lipid profile and carotid intima - media thickness in cerebral ischemia. Indian J Physiol Pharmacol 2014;58:354-64.
22. Lorenz MW, Markus HS, Bots ML, et al. Prediction of clinical cardiovascular evants with carotid intima-media thickness. A systematic review and meta-analysis. Circulation 2007;115: 459-67.

23. Touboul PJ, Hernandez RH, Kucukoglu S, et al. Carotid artery intima thickness, plaque and Framinham cardiovasua score in Asia, Africa/ Middle East latin America: the PARC-AALA Study. Int J Cardiovasc Imaging 2007;235:557-67.

24. Bartels S, Franco AR, Rundek T. Carotid intima-media thickness (cIMT) and plaque from risk assessment and clinical use to genetic discoveries. Perspectives Med 2012;1:139-45.