ORIGINAL ARTICLE

Age should be considered in cut-off values for increased carotid intima-media thickness

Artmış karotis intima-media kalınlığı için sınır değerleri belirlemede yaş göz önünde bulundurulmalıdır

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ABSTRACT

Objective: The current guidelines use a cut-off value of 0.9 mm to define abnormally increased carotid intima-media thickness (C-IMT), regardless of age or gender. This study was conducted to examine the effects of age and gender on C-IMT and cut-off values for C-IMT in different age groups.

Methods: A total of 644 patients with a recorded C-IMT measurement, at least 1 cardiovascular risk factor, and aged between 20 and 90 years were included in the study. Common and internal C-IMT (CC-IMT and IC-IMT) measurements were obtained using carotid ultrasonography (USG). The patients were divided into 5 groups based on age: Group I (20–40 years), Group II (41–50 years), Group III (51–60 years), Group IV (61–70 years), and Group V (>70 years).

Results: The CC-IMT and IC-IMT values were significantly greater as the age of the group increased. Group I to Group V had a median CC-IMT value of 0.70 mm, 0.70 mm, 0.75 mm, 0.75 mm, and 0.85 mm, respectively. The median IC-IMT value for each group was 0.60 mm, 0.65 mm, 0.70 mm, 0.70 mm, and 0.80 mm, respectively. The median CC-IMT value was 50 µm greater than the median IC-IMT value in all groups. Only the CC-IMT value was significantly different in males (0.80±0.20 mm vs. 0.76±0.19 mm; p=0.020). Age, hypertension (HT), smoking, hyperlipidemia, systolic-diastolic blood pressure, and body mass index measures were associated with increased C-IMT. Regression analysis revealed that increased C-IMT was independently associated with age and HT presence. Each decade of life and the presence of HT revealed an incidence of increased C-IMT by 44% and 53%, respectively.

Conclusion: C-IMT significantly increased with age. New, age-appropriate cut-off values are needed for C-IMT assessment. In addition, it was observed that the CC-IMT value was approximately 50 µm greater than the IC-IMT measurement in all age groups. CC-IMT measurements should be included in USG reports.

ÖZET

Amaç: Yaş ve cinsiyetten bağımsız olarak kılavuzlarda artmış karotis intima-media kalınlığı (C-IMT) için sınır değer olarak >0.9 mm kabul edilmektedir. Çalışmamızda, yaş ve cinsiyetin C-IMT üzerine olan etkisini ve değişik yaş gruplarında C-IMT sınır değerlerini araştırmayı planladık.

Yöntemler: Bu geriye dönük çalışmaya 20–90 yaş aralığında en az bir kardiyovasküler risk faktörü olan C-IMT ölçümü yapılmış 644 hasta alındı. Karotid ultrasonografisinde (USG) ana ve internal C-IMT (CC-IMT ve IC-IMT) ölçümleri elde edildi. Hastaların klinik ve demografik parametreleri belirlendi. Çalışmaya dahil edilen hastalar; Grup I (20–40), Grup II (41–50), Grup III (51–60), Grup IV (61–70) ve Grup V (>70) olarak beş gruba ayrıldı.

Bulgular: CC-IMT ve IC-IMT değerleri Grup I'den Grup V'e anlamlı olarak artmaktaydı (p<0.05 her biri). Grup I-II-III-IV-V elde edilen ortanca CC-IMT değeri sırası ile 0.70 mm, 0.70 mm, 0.75 mm, 0.75 mm ve 0.85 mm olduğu bulundu. IC-IMT ortanca değeri ise sırası ile 0.60 mm, 0.65 mm, 0.70 mm, 0.70 mm ve 0.80 mm idi. Tüm yaş gruplarında, ortanca CC-IMT değerinin IC-IMT değerine göre 50 µm daha yüksek olduğu bulundu. Sadece, CC-IMT değerinin erkeklerde anlamlı olarak farklı olduğu saptandı (0.80±0.20 mm ve 0.76±0.19 mm ve p=0.020). Yaş ile birlikte, hipertansiyon (HT), sigara içiciliği ve hiperlipidemi varlığı, sistolik-diyastolik kan basıncı ve vücut kitle indeksi yüksekliği artmış C-IMT ile ilişkili olduğu bulundu. Regresyon analizinde, sadece yaş ve HT varlığı ile artmış C-IMT bağımsız olarak ilişkiliydi. Yaşın her 1-dekat artışı ve HT varlığının sırası ile %44 ve %53 oranında artmış C-IMT varlığını belirlediği tespit edildi.

Sonuç: C-IMT yaş ile beraber anlamlı olarak artar. Bu nedenle, C-IMT için yaşa uygun yeni sınır değerlere ihtiyaç vardır. Ayrıca CC-IMT değerleri tüm yaş gruplarında, IC-IMT ölçümüne göre yaklaşık 50 µm daha yüksektir ve USG raporlarında CC-IMT kullanılmalıdır.

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Atherosclerosis begins in the tunica intima and media layers of the vessel wall, and changes that occur here cause an early increase in intima-media thickness (IMT). In adult patients, IMT evaluation is typically performed from the common carotid (CC) or the internal carotid (IC) artery using ultrasonography (USG). Carotid IMT (C-IMT) is greater in those with cardiovascular (CV) diseases or CV risk factors. Hypertension (HT) due to increased blood pressure, diabetes mellitus (DM) due to glucose intolerance, hyperlipidemia (HL), endothelial dysfunction as a result of cigarette smoking, and coronary artery disease (CAD)-myocardial infarction-stroke presence due to similar risk factors are independent determinants in the measurement IMT.[1–14] Therefore, in diseases such as HT and DM, subclinical target organ involvement or asymptomatic atherosclerosis may be diagnosed early based on IMT measurement, which is recommended by the guidelines.[1,2] In daily practice, an IMT evaluation is frequently used, and is most often based on the carotid artery because it is superficially localized, easily visualized, and most importantly, it is due to the fact that there is already a lot of C-IMT data available.

Abbreviations:

BMI	*Body mass index*
C-IMT	*Carotid IMT*
CAD	*Coronary artery disease*
CC	*Common carotid*
CC-IMT	*Common C-IMT*
CV	*Cardiovascular*
DBP	*Diastolic blood pressure*
DM	*Diabetes mellitus*
ESC	*European Society of Cardiology*
HL	*Hyperlipidemia*
HR	*Heart rate*
HT	*Hypertension*
IC	*Internal carotid*
IC-IMT	*Internal C-IMT*
IMT	*Intima-media thickness*
SBP	*Systolic blood pressure*
USG	*Ultrasonography*

There are conflicting conclusions in the literature about the measurement site to be used and CC-IMT and IC-IMT values in patients with CV risk factors. In some of these studies, CC-IMT increase was assessed, while others examined IC-IMT or bifurcation measurement.[1,3,15–25] Furthermore, evaluation of the HT, DM, HL, and CV protection guidelines revealed no clear data with respect to C-IMT measurement site or cut-off values.[1–4] In fact, the CV protection guideline suggests that routine C-IMT measurements should not be performed in subclinical atherosclerosis screening because the cut-off values are unclear.[3] It was speculated that the IMT values obtained in the CC or IC artery might be different, especially when it was observed that the CC-IMT measurement values were greater than the IC-IMT measurements during routine ultrasonography (USG). The literature data are not clear in this regard. Age and male sex are each a risk factor for CV diseases and are associated with C-IMT increase.[9–12] Independent of age and gender, the current guideline limit for increased C-IMT is >0.9 mm.[1–4] This study was an examination of the theory that different IMT threshold values should be applied according to CV risk factors based on current evidence, clinical experience, and age. The effect of age and gender on both CC-IMT and IC-IMT, and C-IMT cut-off values were analyzed in different age groups.

METHODS

Study population

This retrospective study included 644 patients (314 males, 330 females; mean age: 54.6±14.7 years) of the radiology clinic from August 2017 through September 2018 in order to analyze C-IMT measurement. All of the patients included in the study had at least 1 major CV risk factor. A total of 880 individuals were initially screened; 156 patients were excluded based on essential criteria, and another 80 (11.1% of the remaining patients) were excluded due to the presence of calcific plaques and/or carotid artery stenosis. Patients enrolled in the study were divided into 5 age groups: Group I=20–40 years of age, Group II=41–50, Group III=51–60, Group IV=61–70, Group V=>70. Patients with known secondary or malignant HT, carotid artery stenosis, calcific plaques or a C-IMT ≥1.5 mm, aortic dissection, congestive heart failure, cerebrovascular disease, severe heart valve disease, inflammatory disease, hematological disease, cancer, pregnancy, active thyroid disorder, renal or liver failure were excluded. The Local Ethics Committee approved the study protocol and each participant gave written informed consent (Approval date: 15-Aug-2018, no.: 18-261).

A detailed medical history was recorded and, following a complete physical examination, basic characteristics of age, gender, presence of HT, DM, HL, current smoking status, obesity, body mass index (BMI), heart rate (HR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were also noted.

B-mode ultrasonography evaluation for intima-media thickness

The left and right CC and IC arteries were examined with a high-resolution USG system (Philips EPIQ 7; Philips Healthcare Inc., Andover, MA, USA)

equipped with a 12-5 MHz high-resolution linear converter. All arteries were examined both longitudinally and transversely. All arteries were scanned longitudinally to visualize the IMT on the posterior or distal wall of the artery. All measurements were made on frozen images. The 2 images of the best quality were selected for analysis of each artery. IMT was defined as the distance from the anterior margin of the first echogenic line to the anterior margin of the second line. The first line represents the intima-lumen interface and the second line represents the collagen-containing top layer of adventitia. All IMT values were calculated as the average of 6 measurements. The patients were examined in the supine position, rotating their head 45° for the examination of the carotid artery. The CC-IMT and IC-IMT were measured from 10 to 20 mm proximal before bifurcation for the CC artery, and at the distal segment of the right and left main carotid artery in the distal segment after bifurcation for the IC artery (Fig. 1a-d). The USG examination time was approximately 20 to 30 minutes in all cases. The patients were evaluated by a very experienced radiology specialist with more than 12 years of experience in both conventional and Doppler USG studies and at least 1000 carotid artery Doppler USG procedures a year. Increased CC-IMT or IC-IMT was defined as more than 0.9 mm, as recommended in current guidelines.[1–3,26]

Statistical analysis

All of the analyses were performed using IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp, Armonk, NY, USA) statistical software. The distribution of continuous variables was evaluated and tested for normality using the Kolmogorov-Smirnov test. Continuous variables in the group data were referred to using the mean±SD. Categorical variables were described as a number and percentile. Student's t-test or one-way analysis of variance (ANOVA) was used to compare continuous variables in groups. The Mann-Whitney U test or the Kruskal-Wallis one-way ANOVA test were used for not normally distributed samples. For normally distributed data, the Scheffe and Games-Howell tests were used for multiple comparisons of groups with respect to homogeneity of

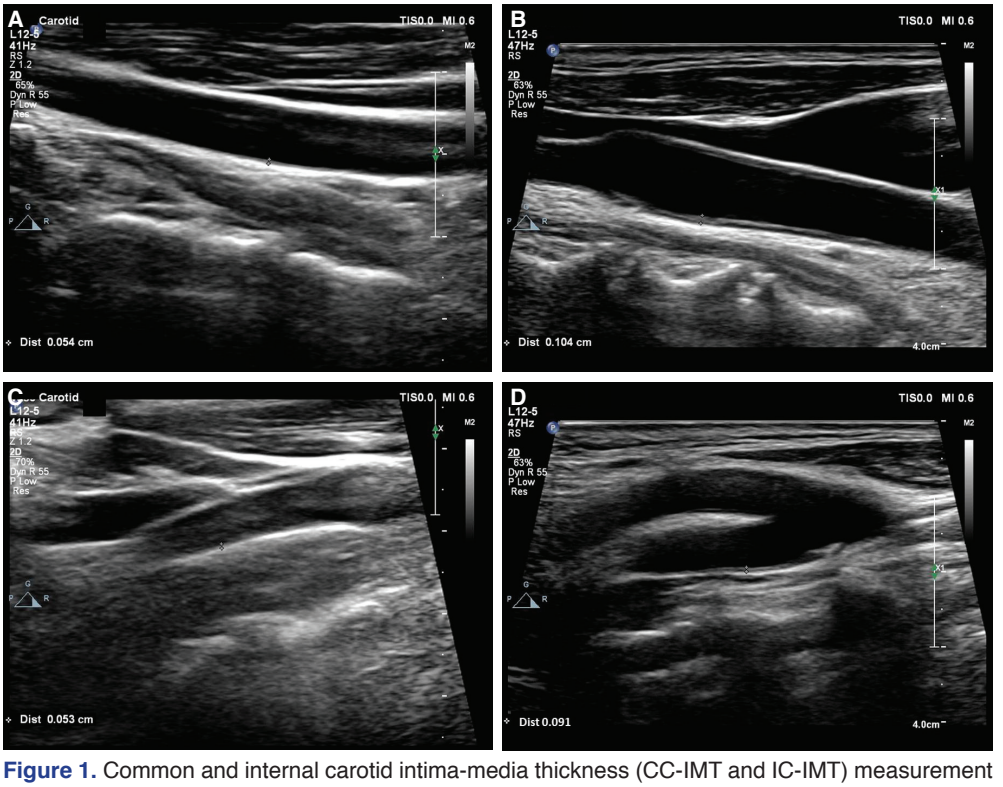


Figure 1. Common and internal carotid intima-media thickness (CC-IMT and IC-IMT) measurement by B-mode ultrasound. **(A)** Normal CC-IMT measurement of 0.54 mm in Group I; **(B)** increased CC-IMT measurement of 1.04 mm in Group V; **(C)** normal IC-IMT measurement of 0.53 mm in Group II; **(D)** increased IC-IMT measurement of 0.91 mm in Group IV.

variances. For non-normally distributed data, a Bonferroni-adjusted Mann-Whitney U test was used for multiple comparisons of groups. The parameters associated with C-IMT were determined using univariate Pearson's and Spearman's correlation analyses. Statistically significant parameters were included in a linear regression analysis, and the parameters with the closest association to the C-IMT were identified. Logistic regression analysis was performed to determine the independent markers among patients with a C-IMT value >0.9 mm. A chi square test was used to compare categorical variables. P<0.05 was considered statistically significant.

RESULTS

The study participants were divided into 5 groups: There were 111 (17%), 147 (23%), 153 (24%), 134 (21%), and 99 (15%) patients in Groups I, II, III, IV, and V, respectively. The patients were also categorized as those with an increased CC-IM T (>0.9 mm) or normal CC-IMT (≤0.9 mm). It was found that 162 patients (25%) had an increased C-IMT. Cohen kappa values that evaluate intraobserver variability were over 90% for all of the C-IMT measurements. All of the clinical and demographic parameters were compared in both groups (age and C-IMT) (Table 1 and 2).

When clinical and demographic findings were compared between the study groups, the presence of HT, DM, smoking, and HL were significantly greater in Group V than in other groups (Table 1). The HR was highest in Group V, with statistical significance between Group V and the other 4 groups (Table 1). The SBP was significantly higher in Group V than in Group I. The BMI was highest in Group II, with statistical significance only between Group II and Group V (Table 1).

Table 1. Clinical and demographic findings according to age groups

Variable	Group I (n=111)	Group II (n=147)	Group III (n=153)	Group IV (n=134)	Group V (n=99)	*p*
Age (years)	33.9±4.7	44.5±5.4	55.8±2.9	64.6±2.4	77.4±6.0	<0.001
Sex (male/female)	49/62	81/66	80/73	59/75	45/54	0.475
Hypertension, n (%)	43 (39)	81 (55)	67 (44)	72 (54)	59 (60)	0.015
Diabetes mellitus, n (%)	12 (11)	34 (23)	36 (24)	38 (28)	46 (47)	<0.001
Current smoker, n (%)	19 (17)	46 (31)	49 (32)	40 (30)	34 (34)	0.033
Hyperlipidemia, n (%)	15 (14)	31 (21)	40 (26)	47 (35)	47 (48)	<0.001
Obesity, n (%)	12 (11)	37 (25)	33 (22)	26 (19)	16 (16)	0.766
Systolic blood pressure (mm Hg)	127±17[α]	132±14	132±12	133±13	135±14	0.033
Diastolic blood pressure (mm Hg)	79±11	81±11	81±12	80±8	80±8	0.064
Heart rate (bpm)	74±10[α,*]	78±12[μ]	81±14[b]	79±15[d]	87±16	<0.001
Body mass index (kg/m^2)	26.2±2.5	27.4±3.8[μ]	26.9±3.4	26.1±3.9	25.5±4.3	<0.001
Mean CC-IMT (mm)	0.71±0.17[α,β,*]	0.73±0.17[μ,‡]	0.78±0.18[b]	0.82±0.21[d]	0.87±0.20	<0.001
Median CC-IMT (mm)	0.70	0.70	0.75	0.75	0.85	
Mean IC-IMT (mm)	0.64±0.16[α,β,*]	0.69±0.18[μ,‡]	0.72±0.17[b]	0.74±0.22[d]	0.84±0.20	<0.001
Median CC-IMT (mm)	0.60	0.65	0.70	0.70	0.80	
CC-IMT or IC-IMT >0.9 mm, n (%)	17 (15)	25 (17)	32 (21)	46 (34)	42 (42)	<0.001
Absolute-ΔC-IMT	0.06±0.04	0.05±0.04	0.06±0.05	0.07±0.06	0.04±0.07	0.065

The values were shown as mean±SD or n (%). Group I=20–40 years, Group II=41–50 years, Group III=51–60 years, Group IV=61–70 years, Group V=over 70 years. Absolute-ΔC-IMT: Difference between CC-IMT and IC-IMT; CC-IMT: Common carotid intima-media thickness; IC-IMT: Internal carotid intima-media thickness.

α: The significant association between Group I and Group V (p<0.05); β: The significant association between Group I and Group IV (p<0.05); *: The significant association between Group I and Group III (p<0.05); ¥: The significant association between Group I and Group II (p<0.05); *μ*: The significant association between Group II and Group V (p<0.05); ‡: The significant association between Group II and Group IV (p<0.05); a: The significant association between Group II and Group III (p<0.05); b: The significant association between Group III and Group V (p<0.05); c: The significant association between Group III and Group IV (p<0.05); d: The significant association between Group IV and Group V (p<0.05).

Table 2. Parameters associated with C-IMT and linear regression analysis for parameters significantly correlated with C-IMT

	Univariate analysis		Multivariate analysis	
	p	r	*p*	β
Common carotid intima-media thickness				
Age (years)	<0.001	0.307	<0.001	0.373
Systolic blood pressure (mm Hg)	<0.001	0.257	<0.001	0.191
Diastolic blood pressure (mm Hg)	0.004	0.117	0.939	0.004
Body mass index (kg/m^2)	0.010	0.102	0.338	0.047
Internal carotid intima-media thickness				
Age (years)	<0.001	0.325	<0.001	0.369
Systolic blood pressure (mm Hg)	<0.001	0.262	<0.001	0.160
Diastolic blood pressure (mm Hg)	0.001	0.131	0.617	0.024
Heart rate (bpm)	0.022	0.092	0.933	0.004
Body mass index (kg/m^2)	0.002	0.121	0.070	0.098

*$R^2_{Adjusted}$=0.183 and 0.195, respectively. C-IMT: Carotid intima-media thickness.

Table 3. Demographic and clinical findings of the subjects with normal and increased carotid intima-media thickness

Variable	Normal C-IMT (n=482)			Increased C-IMT (n=162)			*p*
	n	%	Mean±SD	n	%	Mean±SD	
Age (years)			52.7±14.4			60.3±14.4	<0.001
Sex							
Male	226			88			0.061
Female	256			74			
Hypertension	218	45		104	64		<0.001
Diabetes mellitus	116	24		50	31		0.101
Current smoker	130	27		58	36		0.023
Hyperlipidemia	122	25		58	36		0.010
Obesity	87	18		37	23		0.112
Systolic blood pressure (mm Hg)			129±15			135±13	0.001
Diastolic blood pressure (mm Hg)			79±10			81±10	0.010
Heart rate (bpm)			79±14			80±14	0.677
Body mass index (kg/m^2)			26.3±3.7			27.2±3.5	0.009

CC-IMT: Common carotid intima-media thickness, IC-IMT: Internal carotid intima-media thickness; SD: Standard deviation.

When the patients were grouped by gender, the CC-IMT value was significantly higher in males (0.80±0.20 mm vs 0.76±0.19 mm; p=0.020), and similarly, the IC-IMT was significantly higher in males than in females, but this difference was not statistically significant (0.73±0.19 mm vs 0.71±0.19 mm; p=0.196).

When carotid USG findings were compared between groups, the CC-IMT and IC-IMT values increased significantly from Group I to Group IV (Fig. 2a-d). It was determined that the CC-IMT and the IC-IMT level were statistically different between all study groups (Table 1). The presence of greater C-IMT was significant in Group V in comparison with the other groups (Table 1). The absolute difference between the CC-IMT and IC-IMT (absolute-ΔC-IMT) was similar between all groups.

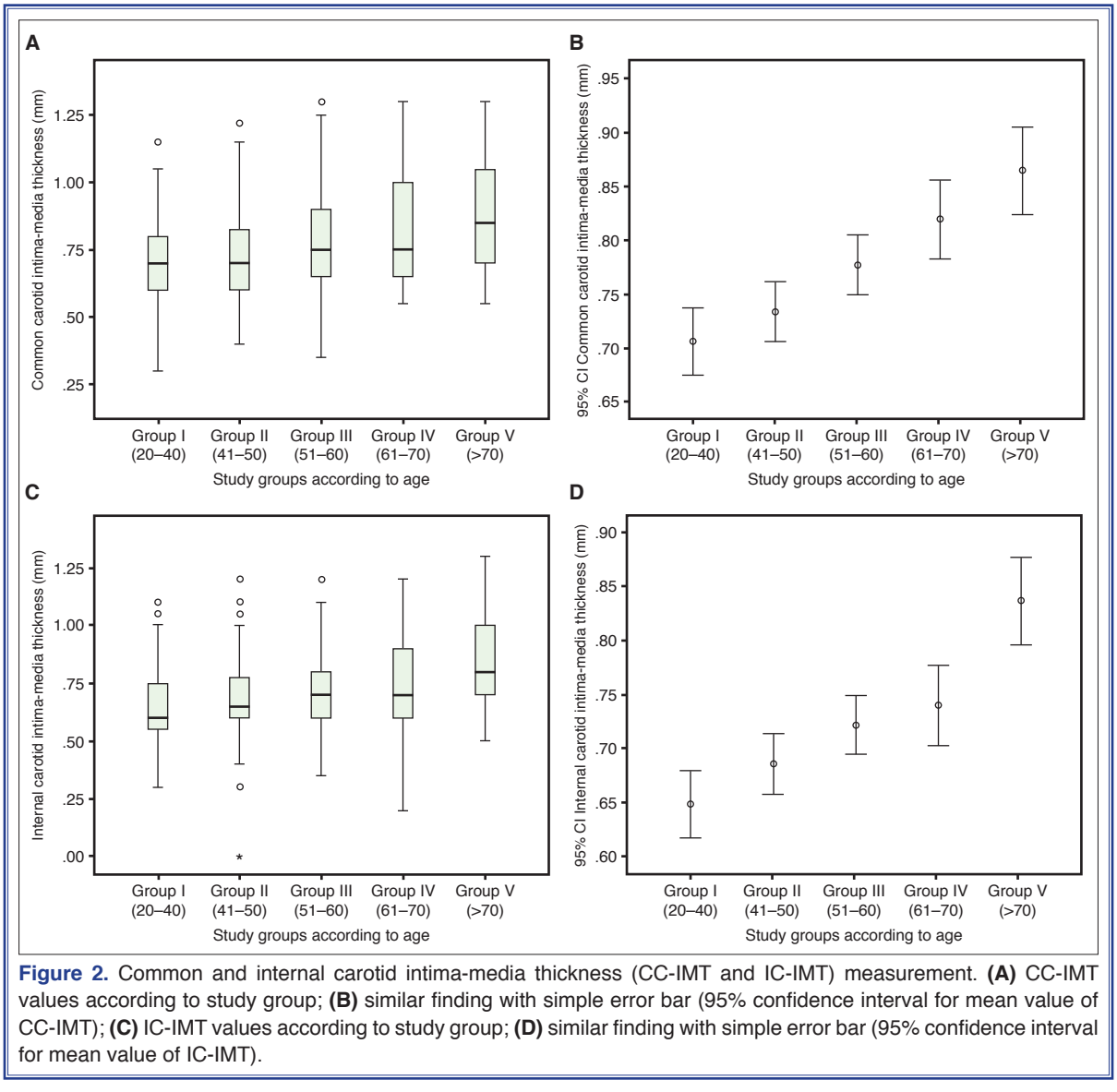


Figure 2. Common and internal carotid intima-media thickness (CC-IMT and IC-IMT) measurement. **(A)** CC-IMT values according to study group; **(B)** similar finding with simple error bar (95% confidence interval for mean value of CC-IMT); **(C)** IC-IMT values according to study group; **(D)** similar finding with simple error bar (95% confidence interval for mean value of IC-IMT).

There was a positive correlation between the IC-IMT and age, SBP, DBP, HR, and BMI. Among these parameters, age and SBP were independent determinants of IC-IMT in linear regression analysis (Table 2, Fig. 3a). Similar findings were found for CC-IMT, with the exception of DBP (Table 2 and Fig. 3b).

Age, the presence of HT, smoking, HL, SBP, DBP, and BMI were significantly higher in the increased C-IMT group, whereas no significant difference was observed with regard to sex, presence of DM, obesity, or HR based on C-IMT measurement (Table 3). The variables that were significantly associated with increased C-IMT in the univariate analysis were entered into logistic regression analyses to predict increased C-IMT. Age and the presence of HT were found to be independently associated with increased C-IMT. In multivariate logistic analysis, age (each decade) and the presence of HT were found to augment the development of C-IMT by 44% and 53.4%, respectively (Table 4).

Table 4. Independent parameters for occurrence of increased carotid intima-media thickness

	Odds ratio	95% Confidence interval	*p*
Age (each 1 year)	1.440	1.266–1.639	<0.001
Hypertension (presence)	0.534	0.340–0.840	0.007

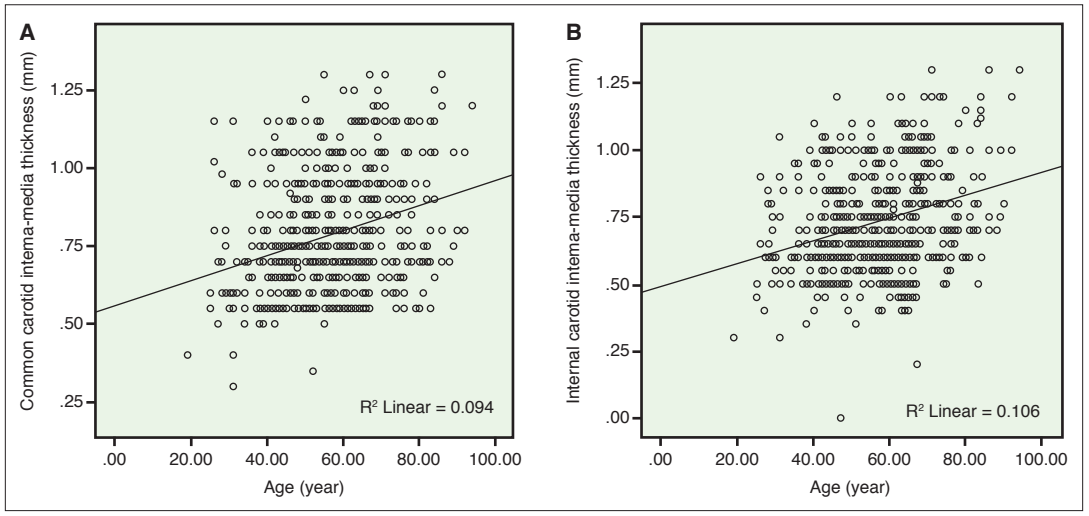


Figure 3. There is a significant correlation between age and **(A)** common carotid intima-media thickness, **(B)** and internal carotid intima-media thickness.

DISCUSSION

The primary outcome of this study is the finding that patient age had an independent effect on C-IMT measurement. The median C-IMT value increased by about 50 μm for each decade after 40 years of age. Another dramatic finding was that CC-IMT values were found to be 50 μm higher than the IC-IMT values in all age groups. The CC-IMT values were also significantly higher in men, as seen in previous data. In addition, we found that apart from age, among other major risk factors, only HT presence was independently associated with increased C-IMT.

The most common cause of death worldwide is atherosclerotic vascular disease and related CV events. Therefore, to provide the best outcomes, atherosclerosis should be detected in the subclinical or asymptomatic phase. An increasing IMT value can be important to recognizing and diagnosing subclinical or asymptomatic atherosclerosis. New USG instruments, high-resolution probes, and automated measurement methods have provided the means for clearer, objective C-IMT imaging.[27,28] IMT measurements have been shown to be a better predictor of target organ involvement of CV risk factors, such as HT, DM, HL, obesity, and subclinical atherosclerosis, in the early stages of patients without major CV events.[1–4]

Arterial disease and risk factors initially led to study of the peripheral arteries, in particular the carotid artery, in the search for clinical signs of CV disease. IMT is not only a premature atherosclerotic zone, but also a smooth muscle hypertrophy/hyperplasia marker. An increased IMT leads to a greater CV risk, regardless of traditional risk factors. The presence and severity of CAD, myocardial infarction, and stroke are also closely related to C-IMT.[1,2,21,29,30,31] It has been clearly shown that HT and other major CV risk factors, such as DM, hyperlipidemia, obesity, cigarette smoking, advanced age, and male gender are associated with a greater C-IMT. Detailed guidelines for diagnosis and treatment of these risk factors have clearly described their role in IMT measurement and determining target organ damage or subclinical atherosclerosis. C-IMT increase (C-IMT >0.9 mm) in HT patients and carotid wall thickening are closely associated with subclinical or asymptomatic organ damage and atherosclerosis, and C-IMT measurement has been recommended as a routine examination. However, while C-IMT measurement is recommended in the guidelines for IMT measurement, it is not clear which of the common, internal, or bifurcation regions of the carotid artery is important. It is stated in the most recent HT guideline that measurements in both the main carotid and bifurcation regions are similar without literature support, and that they are associated with vascular hypertrophy and atherosclerosis, respectively.[1] In the HT guideline, a >0.9 mm C-IMT cut-off value for asymptomatic organ damage was recommended.[1] However, 2 studies have reported that higher IMT values (1.06 mm and 1.16 mm) in elderly patients were useful in CV risk determination.

[21,31] Nonetheless, in daily practice and the current guidelines, a >0.9 mm cut-off is applied for all age groups. This issue was included in the CV disease prevention guideline published in 2016, and C-IMT screening determined by carotid USG is not routinely recommended (Class III recommendation). In the same guideline, a definition, measurement location, variability of IMT measurement, and the lack of standardization at different times and in different people were mentioned. However, with the information obtained from the present study and a literature review, we think that these problems can be resolved with automatic C-IMT measuring devices in the same patient using only the CC-IMT region. Dyslipidemia is another major CV risk factor, and one which increases IMT.[4] However, routine C-IMT measurement is not recommended for all patients with dyslipidemia, but rather only for patients with elevated C-IM; the appropriate treatment is recommended for the presence and treatment of HL according to the lipid panel results and conclusion reached.[4] In patients with familial HL, the situation is different; C-IMT is elevated in these patients and can be regressed with treatment.[4] For this reason, C-IMT measurement may be recommended in the follow-up of these patients. Consistent with previous studies, we found an association between HL and increased C-IMT, but this relationship was not independent in univariate analyses. DM patients also experience increased oxidative stress and endothelial dysfunction with free oxygen radicals and a subsequent IMT increase in vascular remodeling.[2] Increased IMT in DM patients is an important predictor of CV disease and its development.[32,33] C-IMT measurements are recommended for predicting the occurrence of subclinical atherosclerosis or CV disease and CV events, such as HT, in DM patients.[2,34] In our study, C-IMT increases were associated with the presence of DM. However, this relationship was not more important than that of HT.

IMT measurement studies have shown that IMT was greater in male patients.[9–12] However, with increasing age, this difference disappeared and there was no statistical significance in the postmenopausal period.[10] In our study, the CC-IMT value in males was significantly higher than that of females, but this difference was not significant in multivariate analysis. CV risk factors increase with age, and CV risk factors increase IMT. It is therefore normal to have a C-IMT increase in male patients and with increasing age. CC-IMT was thicker than IC-IMT in all age groups in our study. The presence of HT disease or elevated SBP was also independently associated with C-IMT thickness and increased C-IMT status, respectively. Target organ involvement in all age groups was detected earlier in the measurement of CC-IMT than IC-IMT. CC-IMT may be the most prominent vascular localization to demonstrate arterial stiffness. This finding was consistent with ESC 2013 HT guidelines.

There is still no global standard for CC-IMT measurement, but CV disease and CV are still used to determine risk. CC-IMT or IC-IMT is frequently measured in patients who are admitted to radiology clinics for IMT measurement with a carotid USG examination. Occasionally carotid bifurcation, and very rarely, external C-IMT, measurements are taken. Mean or maximum IMT values from different carotid segments are reported in protocols that vary according to the clinic. This difference is also apparent in studies on C-IMT. Studies have reported the anatomical average or maximum value of the CC-IMT, IC-IMT, or bifurcation region measurement, the right or left carotid artery, or the average or measured anatomical region. No standard place of measurement or definition can be found.[15–25] Several cohort studies have shown that IMT values measured from all carotid segments identify CV event development in a similar manner.[15,18–20,35,36] One study indicated that an increased IC-IMT value was a better predictor of a CV event than CC-IMT.[21] In 2 studies conducted by Polak et al.,[20,36] the mean and maximum IC-IMT values were significant in the prediction of CV disease, and CC-IMT and IC-IMT were statistically significant predictors of prevalent CV disease.[36] IC-IMT has been found to better detect CV event development.[20] It was reported in an important study that CC-IMT was significantly affected by factors such as age and BP, while IC-IMT was not, and that IC-IMT is a better indicator of CV risk and atherosclerosis marker.[7] Our study was not study of CV disease or prognosis. However, in our study both CC-IMT and IC-IMT were associated with age and HT presence. This finding did not support the finding of the previous study indicating that IC-IMT was not related to age or BP.

Study limitations

There are some important limitations to this study. Although the number of patients enrolled was sufficient, this is a retrospective study. Patients were not

followed up for this research, and there was no useable data on the effect of treatment on the IMT. Apart from the clinical and demographic data indicated, other clinical and laboratory parameters directly related to IMT could not be evaluated. Among the clinical data, these include assessment of the presence of CAD, which increases IMT. Biochemical parameters include examination of the level of high-sensitivity C-reactive protein, a lipid panel, and inflammatory markers, which have been associated with increased IMT. These evaluations were not performed because our study was retrospective.[37-39] In addition, we did not evaluate the prognosis of the disease in our study. Although some studies have used carotid artery bifurcation for C-IMT measurement, we did not measure this area because of the anatomical structure of this region and inadequate literature data.[37] C-IMT can be measured automatically and semi-automatically with new software programs, resulting in a lower average value than with manual measurement.[27,28] This automatic measurement removes operator dependence and makes it more useful for repetitive measurements; however, our high-resolution device did not have this software program. Automatically or semi-automatically measured IMT values would lead to even more objective and meaningful results.

Conclusion

According to our study results and those of previous studies, IMT values increase with age and age is a very important risk factor associated with IMT. Rather than guidelines with a constant IMT value to determine an increased IMT, we believe it would be more useful to give a cut-off value for specific ages. The median C-IMT value obtained in patients over 70 years of age was close to the guideline value. New values are needed for patients over 70 years of age, especially if they can be diagnosed with an elevated C-IMT. The question of whether IMT assessment should be performed from the CC or the IC artery is still unclear. According to our study, the CC-IMT value was increased but without significance in the IC-IMT (<0.9 mm). The CC-IMT is more useful than the IC-IMT in demonstrating vascular organ involvement in the relatively early stages of CV diseases or the presence of risk factors. CC-IMT values should be recorded in the carotid USG examinations required in patient follow-up for target organ involvement, and these values should be used in follow-up treatment. Repeat IMT measurement should be done in the same region. Our findings should be supported by new studies conducted based on clinical knowledge and the vascular anatomy. The guidelines should also be updated in this regard. There is a need for new, prospective, multicenter studies on this subject.

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REFERENCES

1. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–104.
2. Authors/Task Force Members, Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013;34:3035–87.
3. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–81.
4. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, Hoes AW, et al; ESC Scientific Document Group. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. Eur Heart J 2016;37:2999–3058.
5. Nezu T, Hosomi N, Aoki S, Matsumoto M. Carotid Intima-Media Thickness for Atherosclerosis. J Atheroscler Thromb 2016;23:18–31.
6. Brohall G, Odén A, Fagerberg B. Carotid artery intima-media thickness in patients with Type 2 diabetes mellitus and impaired glucose tolerance: a systematic review. Diabet Med

2006;23:609–16.
7. Al-Shali K, House AA, Hanley AJ, Khan HM, Harris SB, Mamakeesick M, et al. Differences between carotid wall morphological phenotypes measured by ultrasound in one, two and three dimensions. Atherosclerosis 2005;178:319–25.
8. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. JAMA 2003;290:2277–83.
9. Su TC, Chien KL, Jeng JS, Chen MF, Hsu HC, Torng PL, et al. Age- and gender-associated determinants of carotid intima-media thickness: a community-based study. J Atheroscler Thromb 2012;19:872–80.
10. Sinning C, Wild PS, Echevarria FM, Wilde S, Schnabel R, Lubos E, et al.Sex differences in early carotid atherosclerosis (from the community-based Gutenberg-Heart Study). Am J Cardiol 2011;107:1841–7.
11. Howard G, Sharrett AR, Heiss G, Evans GW, Chambless LE, Riley WA, et al. Carotid artery intimal-medial thickness distribution in general populations as evaluated by B-mode ultrasound. ARIC Investigators. Stroke 1993;24:1297–304.
12. Mannami T, Konishi M, Baba S, Nishi N, Terao A. Prevalence of asymptomatic carotid atherosclerotic lesions detected by high-resolution ultrasonography and its relation to cardiovascular risk factors in the general population of a Japanese city: the Suita study. Stroke 1997;28:518–25.
13. Tan TY, Lu CH, Lin TK, Liou CW, Chuang YC, Schminke U. Factors associated with gender difference in the intima-media thickness of the common carotid artery. Clin Radiol 2009;64:1097–103.
14. Fisicaro M, Da Col PG, Tonizzo M, Fonda M, Bollini M, Cattin L. Early carotid atherosclerosis in asymptomatic adults with primary moderate hypercholesterolemia: a case-control study. Atherosclerosis 1994;106:255–61.
15. Cao JJ, Arnold AM, Manolio TA, Polak JF, Psaty BM, Hirsch CH, et al. Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality: the Cardiovascular Health Study. Circulation 2007;116:32–8.
16. Iglesias del Sol A, Bots ML, Grobbee DE, Hofman A, Witteman JC. Carotid intima-media thickness at different sites: relation to incident myocardial infarction; The Rotterdam Study. Eur Heart J 2002;23:934–40.
17. Rosvall M, Janzon L, Berglund G, Engström G, Hedblad B. Incidence of stroke is related to carotid IMT even in the absence of plaque. Atherosclerosis 2005;179:325–31.
18. Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke 2006;37:87–92.
19. Folsom AR, Kronmal RA, Detrano RC, O'Leary DH, Bild DE, Bluemke DA, et al. Coronary artery calcification compared with carotid intima-media thickness in the prediction of cardiovascular disease incidence: the Multi-Ethnic Study of Atherosclerosis (MESA). Arch Intern Med 2008;168:1333–9.
20. Polak JF, Pencina MJ, Pencina KM, O'Donnell CJ, Wolf PA, D'Agostino RB Sr. Carotid-wall intima-media thickness and cardiovascular events.N Engl J Med 2011;365:213–21.
21. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med 1999;340:14–22.
22. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol 1997;146:483–94.
23. Polak JF, Szklo M, Kronmal RA, Burke GL, Shea S, Zavodni AE, et al. The value of carotid artery plaque and intima-media thickness for incident cardiovascular disease: the multi-ethnic study of atherosclerosis. J Am Heart Assoc 2013;2:e000087.
24. van der Meer IM, Bots ML, Hofman A, del Sol AI, van der Kuip DA, Witteman JC. Predictive value of noninvasive measures of atherosclerosis for incident myocardial infarction: the Rotterdam Study. Circulation 2004;109:1089–94.
25. Johnsen SH, Mathiesen EB, Joakimsen O, Stensland E, Wilsgaard T, Løchen ML, et al. Carotid atherosclerosis is a stronger predictor of myocardial infarction in women than in men: a 6-year follow-up study of 6226 persons: the Tromsø Study. Stroke 2007;38:2873–80.
26. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the Management of Arterial Hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens 2007;25:1105–87.
27. Novo G, Di Miceli R, Orlando D, Lunetta M, Pugliesi M, Fiore M, et al. Carotid intima-media thickness measurement through semi-automated detection software and analysis of vascular walls. Int Angiol 2013;32:349–53.
28. Shenouda N, Proudfoot NA, Currie KD, Timmons BW, MacDonald MJ. Automated ultrasound edge-tracking software comparable to established semi-automated reference software for carotid intima-media thickness analysis. Clin Physiol Funct Imaging 2018;38:396–401.
29. Bots ML, Hoes AW, Koudstaal PJ, Hofman A, Grobbee DE. Common carotid intima-media thickness and risk of stroke and myocardial infarction: the Rotterdam Study. Circulation 1997;96:1432–7.
30. Nambi V, Chambless L, Folsom AR, He M, Hu Y, Mosley T, et al. Carotid intima-media thickness and presence or absence of plaque improves prediction of coronary heart disease risk: the ARIC (Atherosclerosis Risk In Communities) study. J Am

Coll Cardiol 2010;55:1600–7.

31. Zanchetti A, Bond MG, Hennig M, Neiss A, Mancia G, Dal Palù C, et al; European Lacidipine Study on Atherosclerosis investigators. Calcium antagonist lacidipine slows down progression of asymptomatic carotid atherosclerosis: principal results of the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind, long-term trial. Circulation 2002;106:2422–7.
32. Flammer AJ, Anderson T, Celermajer DS, Creager MA, Deanfield J, Ganz P, et al. The assessment of endothelial function: from research into clinical practice. Circulation 2012;126:753–67.
33. Vlachopoulos C, Aznaouridis K, Stefanadis C. Prediction of cardiovascular events and all-cause mortality with arterial stiffness: a systematic review and meta-analysis. J Am Coll Cardiol 2010;55:1318–27.
34. Bernard S, Sérusclat A, Targe F, Charrière S, Roth O, Beaune J, Berthezène F, Moulin P. Incremental predictive value of carotid ultrasonography in the assessment of coronary risk in a cohort of asymptomatic type 2 diabetic subjects. Diabetes Care 2005;28:1158–62.
35. NIPPON DATA80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. Circ J 2006;70:1249–55.
36. Polak JF, Pencina MJ, Meisner A, Pencina KM, Brown LS, Wolf PA, et al. Associations of carotid artery intima-media thickness (IMT) with risk factors and prevalent cardiovascular disease: comparison of mean common carotid artery IMT with maximum internal carotid artery IMT. J Ultrasound Med 2010;29:1759–68.
37. Sitzer M, Markus HS, Mendall MA, Liehr R, Knorr U, Steinmetz H. C-reactive protein and carotid intimal medial thickness in a community population. J Cardiovasc Risk 2002;9:97–103.
38. Hulthe J, Fagerberg B. Circulating oxidized LDL is associated with subclinical atherosclerosis development and inflammatory cytokines (AIR Study). Arterioscler Thromb Vasc Biol 2002;22:1162–7.
39. Kozàkovà M, Palombo C, Morizzo C, Nolan JJ, Konrad T, Dekker JM, et al. Gender-specific differences in carotid intima-media thickness and its progression over three years: a multicenter European study. Nutr Metab Cardiovasc Dis 2013;23:151–8.

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