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Apolipoproteins A1 and B and their ratio in acute ischemic stroke patients with intracranial and extracranial arterial stenosis: an Egyptian study

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Abstract

Background: Apolipoprotein A1 and B and their ratio are considered a better biomarker for cardiovascular diseases than a lipid profile, but this previous finding is not proved to cerebrovascular ischemic diseases. The aim of this study is to assess the relation between apolipoprotien A1 and B and their ratio to intra- and extracranial carotid atherosclerosis in patients with ischemic acute stroke.

Methods: 90 Egyptian patients with acute ischemic stroke are included in the study, and they have been classified into 3 groups: group 1 includes 30 patients with intracranial stenosis, group 2 includes 30 patients with extracranial arterial stenosis, and group 3 includes 30 patients with non-arterial stenosis. Patients were subjected to clinical assessment, routine laboratory measures, and Color-Coded Duplex Sonography for extracranial and intracranial arteries. The measurement of serum levels of apolipoproteins A1 and B was done using enzyme-linked immuno-sorbent assay (ELISA).

Results: A statistically significant difference was found between patient groups as regards the frequency of abnormal serum LDL-cholesterol ($p = 0.04$), being elevated in patients with extracranial stenosis ($p = 0.01$). There was a significant difference between patients groups as regards the frequency of abnormal serum HDL-cholesterol ($p = 0.02$), being lower in patients with extracranial stenosis. High Apo B/A1 ratio was an independent risk factor for intracranial arterial stenosis ($p = 0.045$). An abnormal elevation of serum LDL cholesterol was an independent risk factor of extracranial arterial stenosis ($p = 0.021$).

Conclusion: Apo B/A1 ratio is an independent risk factor for intracranial arterial stenosis, while serum LDL cholesterol is an independent risk factor for extracranial arterial stenosis. Apo B/A1 ratio and serum LDL cholesterol are reliable serum biomarkers for cranial arterial stenosis in acute ischemic stroke patients.

Keywords: Apolipoprotein A1, Apolipoprotein B, Atherosclerosis, Intracranial stenosis, Extracranial stenosis

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Introduction

Cerebral artery stenosis is known as a primary cause of stroke. It can be divided into intracranial arterial stenosis (ICAS), extracranial arterial stenosis (ECAS), and combined intracranial and extracranial arterial stenosis. Intracranial arterial stenosis causes approximately 8 to 12% of ischemic stroke. The most prevalent type of extracranial arterial stenosis is carotid artery stenosis; it represents about 15% of ischemic stroke [1].

The distribution of carotid artery stenosis was different among races. It was known that intracranial carotid artery stenosis is more common in the African-American and Asian population while extracranial stenosis is more predominant in Caucasians. Meticulous studies were done to detect the racial difference as a risk of stroke, and now, it is found that intracranial stenosis is a risk factor for stroke in Caucasian which is a different finding than that was reported previously [2]. In Egypt, the ICAD is more prevalent than ECAD as 67% has intracranial artery stenosis and 27% has asymptomatic intracranial carotid artery stenosis in a study done by Moustafa and colleagues in Egyptian patients with acute ischemic stroke within 2 days of onset [3].

The natural history of intracranial carotid atherosclerotic disease (ICAD) was well-established in the Warfarin-Aspirin Symptomatic Intracranial Disease Trial (WASID), which detects that severe stenosis > 70% leads to a higher incidence of stroke that is about)19%(in the territory of the symptomatic stenotic artery despite antiplatelet management if it compared to lower incidence of stroke (8%) in patients with stenosis < 70% [4].

Few studies were done to evaluate the risk for intracranial carotid stenosis which may be related to the poverty of non-invasive technics that can visualize the intracranial carotid artery. Nowadays, many non-invasive imaging techniques were developed like trans-cranial Doppler ultrasonography (TCD), magnetic resonance angiography (MRA), and computed tomography angiography (CTA) [5].

Apolipoproteins A1 and B are structural proteins for lipoproteins, and it is considered a better predictor for stroke than the ordinary lipid profile. Apolipoprotein A1is a structural protein for high-density lipoprotein (HDL), which transfers cholesterol from the peripheral tissue to the liver for final excretion (it has an anti-atherogenic effect). Apolipoprotein B is a structural protein for very low- low-density lipoprotein (VLDL, LDL), and it transfers the lipid from the liver to the gut and other tissues for peripheral utilization (atherogenic effect). Apo B/A1 ratio which is the ratio between atherogenic to anti-atherogenic particles is a better predictor for risk of coronary vascular disease than the known ordinary lipid and lipoprotein profile [6–8].

Few studies were done to detect the relation between apolipoproteins and carotid atherosclerosis by its subtypes intracranial and extracranial. This study was conducted to investigate the relation of apolipoproteins A1 and B, and their ratio to intracranial and extracranial atherosclerotic arterial stenosis in a sample of Egyptian patients with acute ischemic stroke.

Methods

This is a cross-sectional study enrolled 90 Egyptian stroke patients, in the period from January 2018 to April 2019. Patients were collected within 7 days from the onset of acute ischemic stroke. The aim and procedures of the study were explained to all patients, and informed oral consents were taken prior to participation to ensure complete satisfaction.

Inclusion criteria were patients (of both sexes) presented with acute ischemic cerebral infarction within 7 days from the onset, age above 45 years, and stable and fully conscious patients. Exclusion criteria were cardio-embolic diseases (as atrial fibrillation, rheumatic heart disease, artificial valve, intracardiac thrombus or tumor, cardiomyopathy, myocardial infarction within 3 months), severe liver or renal insufficiency, stroke caused by non-atherosclerotic vascular stenosis, and intake of lipid-modifying therapy.

Patients were classified into three groups: group 1 included 30 patients with intracranial arterial stenosis, group 2 included 30 patients with extracranial arterial stenosis, and group 3 included 30 patients without arterial stenosis.

Patients were submitted to full general and neurological examination. The initial severity of stroke was measured by the National Institutes of Health Stroke Scale (NIHSS) [7]. Non-contrast brain computed tomography (CT) (computed tomography, Toshiba, Aquilion; 64 slices, Japan, 2005) and/or magnetic resonance imaging (MRI) (magnetic resonance imaging, Philips, Achiva and Intera; 1.5 Tesla, Holland, 2003) to confirm the diagnosis of acute ischemic stroke.

Color-coded Duplex sonography for intracranial and extracranial arteries has done using (Philips iU22 machine, Bothell, WA, USA, 2008). The patients lie down in the supine or semi-supine position with the head slightly hyperextended and rotated 45° away from the side being examined. A high-frequency (7 to 10 MHz) linear array transducer was employed to scan the carotid from the most proximal common carotid artery (CCA) to the internal carotid artery (ICA) as far as the mandible permitted. Peak systolic velocities (PSVs) were measured in the common and internal carotid arteries, and when stenosis was detected, the velocities were measured at the maximal stenotic area. The intracranial arteries were evaluated using 2 MHz phased array transducer. Each insonated artery was investigated by peak systolic velocity (PSV) used for the presence of stenosis or occlusion, flow direction (ante-grade or reversed) [9, 10].

Routine laboratory investigations including complete blood count, international neutralization rate, partial thromboplastin time, kidney functions, liver functions, fasting, 2H PP blood sugar, and lipid profile. Dyslipidemia was defined as fasting serum total cholesterol of ≥ 200 mg/dl, LDL cholesterol of ≥ 130 mg/dl, and HDL cholesterol of ≤ 40 mg/dl for men and ≤ 50 mg/dl for women or a triglyceride concentration of ≥ 150 mg/dl [11].

Measurement of serum levels of apolipoproteins B and A1 and their ratio: the assay of apolipoproteins B and A1 levels was done for all patients using enzyme-linked immuno-sorbent assay (ELISA) technique. Venous blood samples were collected then centrifuged to get serum. The human apolipoproteins B and A1 kits were used for the quantitative measurement of levels of apolipoproteins B and A1 in serum using the competitive immunoassay technique. Detection range of the kit was 16 ng/ml–1000 ng/ml for Apo B and 1.2 ng/ml–80 ng/ml for Apo A1.

In conditions at which there was a problem in the assay like giving an error as the assay range is not within the detection range of the kit, dilution of the sample done, and then reassessment done. The value of reassessment is then multiplied by the percent of diluting fluid used giving us the actual level which is higher than the detection range [12].

Statistical analysis
Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 25 (IBM Corp., Armonk, NY, USA). Data was summarized using the mean and standard deviation for quantitative variables and frequencies and relative frequencies for categorical variables. Comparisons between groups were done using unpaired *t* test or analysis of variance (ANOVA) with multiple comparisons post hoc test in normally distributed quantitative variables while nonparametric Kruskal-Wallis test and Mann-Whitney test were used for non-normally distributed quantitative variables. Logistic regression was done to detect independent predictors for intracranial and extracranial arterial stenosis [13, 14].

Results
Demographic data
Group I included 15 female (50%) and 15 male patients (50%). Their age ranged from 45 to 80 years with a mean of 57.70 ± 10.81 years. Group II included 15 female (50%) and 15 male patients (50%). Their age ranged from 49 to 78 years with a mean of 62.53 ± 8.25 years. Group III included 12 female (40%) and 18 male patients (60%). Their age ranged from 45 to 84 years with a mean of 60.40 ± 10.37 years. There was no statistically significant difference between the three groups as regards

the mean age and sex distribution (p = 0.17, 0.67, respectively).

Clinical characteristics of patients
NIHSS scores ranged from 2 to 20 in group I, from 2 to 23 in group II, and from 2 to 23 in group III, with no significant difference between the three groups (*p* = 0.10). Frequency of hypertension, diabetes mellitus, and current smoking are shown in Table 1.

Serum apolipoprotein B ranged from 679 to 1472 ng/ml with a mean of 1035.07 ± 246.37 ng/ml in group I, from 386 to 1602 ng/ml with a mean of 1048.70 ± 282.16 ng/ml in group II and from 440 to 1275 ng/ml with a mean of 943.90 ± 206.42 ng/ml in group III.

Serum apolipoproteins A1 ranged from 21.5 to 87.5 ng/ml with a mean value of 47.78 ± 14.97 ng/ml in group I, from 25 to 130 ng/ml with a mean of 49.68 ± 20.29 ng/ml in group II and from 35 to 130 ng/ml with a mean of 51.32 ± 18.83 ng/ml in group III.

Apo B/A1 ratio ranged from 14.1 to 31.7 with a mean of 22.64 ± 4.64 in group I, from 11.30 to 36.40 with a mean of 22.48 ± 5.72 in group II, and from 9.4 to 28.9 with a mean of 19.86 ± 5.49 in group III. There was a statistically significant difference between patients groups as regards the frequency of abnormal serum LDL cholesterol (*p* = 0.04). Moreover, there was insignificant difference between the three groups as regards the frequency of abnormal serum HDL cholesterol (*p* = 0.07). No significant difference was found as regards total serum cholesterol (*p* = 0.1) or triglycerides (*p* = 0.5) (Table 2, Fig. 1).

Total serum cholesterol ranged from 118 to 294 mg/dl with a mean 196.40 ± 48.78 mg/dl in group I, from 87 to 283 mg/dl with a mean 196 ± 58.62 mg/dl in group II, and from 71 to 335 mg/dl with a mean 185.90 ± 54.56 mg/dl in group III. Elevated total serum cholesterol was found in 14 patients (46.7%) of group I, 15 patients (50%) of group II, and 8 patients (26.7%) of group III (Table 2).

Serum LDL cholesterol ranged from 28 to 222 mg/dl with a mean 123.50 ± 45.64 mg/dl in group I, from 38 to

Table 1 Frequency of hypertension, diabetes, and smoking among patients groups

		Group I		Group II		Group III		P value
		Count	%	Count	%	Count	%	
Hypertension	Yes	23	76.7	22	73.3	21	70	0.8
	No	7	23.3	8	26.7	9	30	
Diabetes	Yes	16	53.3	16	53.3	11	36.7	0.3
	No	14	46.7	14	46.7	19	63.3	
Smoking	Yes	10	33.3	15	50	13	43.3	0.4
	No	20	66.7	15	50	17	56.7	

Table 2 Comparison of frequency of abnormal lipid profile between patients groups

Serum lipids		Group I (intracranial stenosis)		Group II (extracranial stenosis)		Group III (no stenosis)		P value
		Count	%	Count	%	Count	%	
Cholesterol (mg/dl)	Normal	16	53.3	15	50	22	73.3	0.1
	Abnormal	14	46.7	15	50	8	26.7	
LDL-cholesterol (mg/dl)	Normal	15	50	13	43.3	22	73.3	0.04*
	Abnormal	15	50	17	56.7	8	26.7	
HDL-cholesterol (mg/dl)	Normal	9	30	5	16.7	13	43.3	0.07
	Abnormal	21	70	25	83.3	17	56.7	
Triglycerides (mg/dl)	Normal	18	60	19	63.3	22	73.3	0.5
	Abnormal	12	40	11	36.7	8	26.7	

*Significant

197 mg/dl with a mean 119.13 ± 42.99 mg/dl in group II, and from 38 to 223 mg/dl with a mean 118.03 ± 37.52 mg/dl in group III. Elevated serum LDL cholesterol was found in 15 patients (50%) of group I, 17 patients (56.7%) of group II, and 8 patients (26.7%) of group III (Table 2).

Serum HDL cholesterol ranged from 23 to 60 mg/dl with a mean 39.93 ± 9.06 mg/dl in group I, from 26 to 60 mg/dl with a mean 37.30 ± 8.54 mg/dl in group II, and from 16 to 62 mg/dl with a mean 40.53 ± 12.48 mg/dl in group III. Low serum HDL cholesterol was found in 21 patients (70%) of group I, 25 patients (83.3%) of group II, and 17 patients (56.7%) of group III (Table 2).

Serum triglycerides ranged from 57 to 429 mg/dl with a mean 169.23 ± 98.31 mg/dl in group I, from 39 to 324 mg/dl with a mean 133.20 ± 68.11 mg/dl in group II, and from 36 to 392 mg/dl with a mean 137.67 ± 79.46 mg/dl in group III. Elevated serum triglycerides were found in 20 patients (66.7%) of group I, 15 patients (50%) of group II, and 17 patients (56.7%) of group III (Table 2).

There was a statistically significant difference between patients with extracranial stenosis and no stenosis as regards the frequency of abnormal serum LDL cholesterol ($p = 0.01$) and serum HDL-cholesterol ($p = 0.02$), as serum LDL cholesterol was higher, and serum HDL cholesterol was lower in patients with extracranial stenosis. A statistically insignificant difference in serum LDL cholesterol was found between patients with intracranial stenosis and no-stenosis group ($p = 0.06$), as abnormal elevation of serum LDL cholesterol was encountered more in the intracranial stenosis group. There was no statistically significant difference between patients with intracranial stenosis and extracranial stenosis as regards the serum LDL cholesterol ($p = 0.6$) or HDL cholesterol ($p = 0.2$).

There was no statistically significant difference between patients with intracranial stenosis, extracranial stenosis, and no-arterial stenosis as regards the mean serum apolipoprotein B ($p = 0.2$) or apo-lipoprotein A1 ($p = 0.7$). There is an insignificant difference in Apo B/A1 ratio between patients groups ($p = 0.07$) (Table 3).
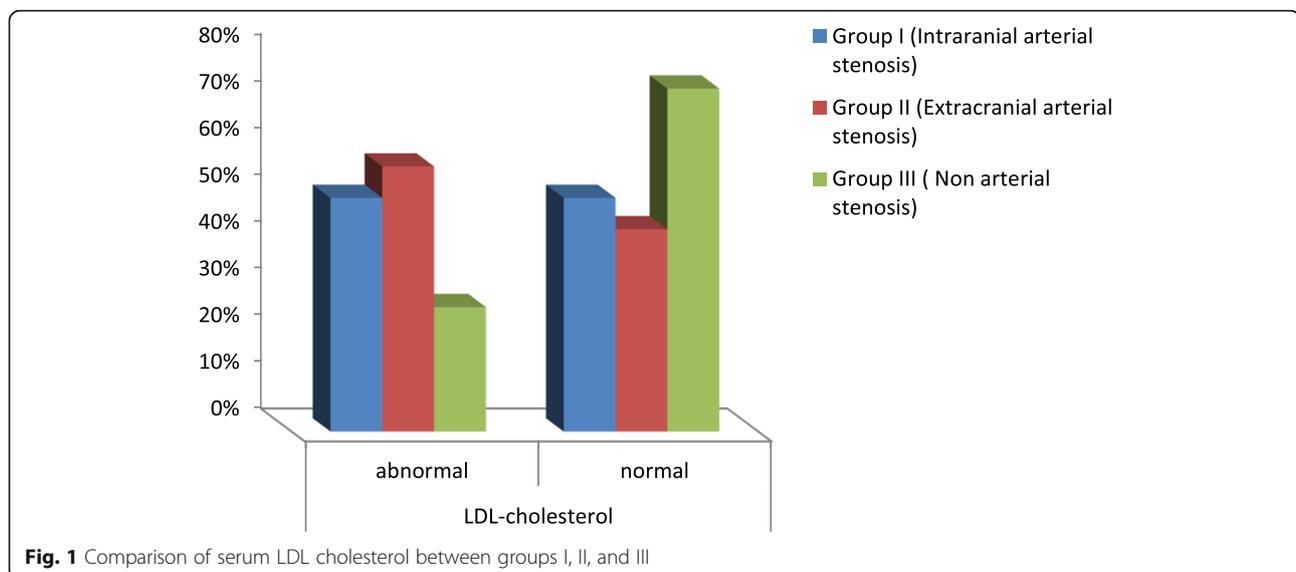
Fig. 1 Comparison of serum LDL cholesterol between groups I, II, and III

Table 3 Comparison of mean serum levels of apolipoproteins B, A1, and their ratio between patients groups

	Group I (intracranial stenosis)		Group II (extracranial stenosis)		Group III (no-arterial stenosis)		p value
	Mean	SD	Mean	SD	Mean	SD	
Apolipoprotein B (ng/ml)	1035.07	246.37	1048.70	282.16	943.90	206.42	0.2
Apolipoprotein A1 (ng/ml)	47.78	14.97	49.68	20.29	51.32	18.83	0.7
Apo B/Apo A1 ratio	21.66	4.64	21.1	5.72	18.39	5.49	0.07

No significant correlation was found between serum apolipoprotein B, apolipoprotein A1 and LDL cholesterol, and HDL cholesterol in groups I, II, or III ($p > 0.05$). Multivariate logistic regression analysis revealed that high Apo B/A1 ratio is an independent risk factor for intracranial arterial stenosis ($p = 0.04$), and abnormal serum LDL cholesterol is an independent risk factor for extracranial arterial stenosis ($p = 0.02$), see Tables 4 and 5.

Discussion

High-lipid profile is associated with atherosclerosis in general but whether a particular lipid profile is associated with extra- and/or intracranial carotid artery stenosis are not well studied [15]. In the present study, we try to find a relation between different lipid parameters and degree of intra- and/or extracranial carotid stenosis in a sample of Egyptian patients presented by acute stroke.

The present study showed a statistically significant difference between extracranial atherosclerotic arterial stenosis and non-arterial stenosis regarding serum LDL cholesterol, and patients with extracranial arterial stenosis had the higher frequency of abnormal LDL cholesterol (high LDL–C). Also, in the present study, abnormal serum LDL cholesterol (high LDL-C) found to be an independent risk factor for extracranial atherosclerotic arterial stenosis, a finding which was in agreement with several previous studies [16, 17].

The current study showed a statistically significant difference between extracranial atherosclerotic arterial stenosis and non-arterial stenosis regarding serum HDL cholesterol with patients with extracranial arterial stenosis had the higher frequency of abnormal HDL cholesterol (low HDL–C). This goes in agreement with Kim and collegues and Junyent and collegues [18, 19]. On the contrary, other studies Lei and colleagues and Qian and colleagues, who found that low HDL level was

associated with intracranial stenosis, and this may be explained by ethnic variations [15, 20].

The current study revealed no statistical difference between extracranial arterial stenosis, intracranial arterial stenosis, and non-arterial stenosis as regards the frequency of clinical risk factors: hypertension, diabetes, or smoking. This goes in agreement with Kim and colleagues, El Zayat and colleagues and Yang and colleagues [18, 21, 22] who found that the location of cerebral atherosclerosis in extracranial or intracranial arteries is not explained by differences in the known modifiable risk factors among the same ethnic group. It means that modifiable risk factors (diabetes, hypertension, and smoking) have equivalent role in pathogenesis of intracranial and extracranial atherosclerosis.

There was a comprehensive meta-analysis study done by Ding and colleagues [23], on Asian population, investigated the effect of risk factors including age, sex, hypertension, diabetes, dyslipidemia, smoking, and metabolic syndrome (Met.S) on the location of atherosclerotic stenosis like ICAS and ECAS. This meta-analysis revealed that female sex and MetS were more linked to ICAS, while smoking and hyperlipidemia were more linked to ECAS. There was no significant difference between ICAS and ECAS in terms of age, hypertension, and diabetes. The difference between our study and other studies can be explained in terms of sample size and ethnic variations.

In the present study, Apo B/A1 ratio was an independent risk factor for intracranial atherosclerotic arterial stenosis compared to extracranial atherosclerotic arterial stenosis and non-arterial stenosis, a finding which was in agreement with several previous studies. Two Korean studies done by park and colleagues, [24, 25] who found that a higher Apo/A1 ratio is a prognostic factor for ICAS rather than extracranial atherosclerotic stenosis or no cerebral atherosclerotic stenosis and Apo B/A1 ratio

Table 4 Multivariate logistic regression analysis model of independent factors for intracranial arterial stenosis

		P value	OR	95% C.I.	
				Lower	Upper
Intracranial arterial stenosis	Apo B/Apo A1 ratio	0.045*	1.118	1.002	1.246

OR odds ratio, *significant, CI confidence interval

Table 5 Multivariate logistic regression analysis model of independent factors of intracranial arterial stenosis

		P value	OR	95% C.I.	
				Lower	Upper
Extracranial arterial stenosis	Abnormal LDL-cholesterol	0.021*	3.596	1.216	10.638

OR odds ratio, *significant

might be a marker for ICAS in Asian patients with stroke. Kim and colleagues [26] also found that low Apo B/A1 ratio is associated with stability of angiographic symptomatic intracranial atherosclerotic stenosis.

There were other studies showed that Apo B/A1 ratio is associated with extracranial not intracranial stenosis [27, 28]. The absence of correlation between Apo B/A1 ratio and LDL-C or HDL-C can be explained by that HDL, and LDL not accurately reflects the concentration of the circulating lipoproteins as these molecules exposed to changes in their size and composition so sometimes lack of correlation between Apo B/A1 ratio and LDL-C or HDL-C could be found [29]. These contradictory findings may be related to differences in study design or ethnic variation as atherosclerosis is a multifactorial disorder with environmental, demographic, and genetic factors leads to its development.

Our study has some limitations. First is the small sample size. Second, its design was cross-sectional, so we could not directly assess the prognostic impact of different lipid profiles and cerebrovascular risk factors in patients with symptomatic intracranial and/or extracranial atherosclerosis. Third, our study population was hospital based, so it may not accurately reflect what happens in the general population. Therefore, revealed results are clearly exploratory and preliminary. Equal sex distribution in the three groups also adds limitation to the study as sex distribution among patients with extracranial and intracranial stenosis.

With the previous limitations, the current study revealed that Apo B/A1 ratio and serum LDL cholesterol can be used as reliable biomarkers for ICAS and ECAS, respectively. Future research including a larger sample size is warranted for further clarification of the relation between apolipoproteins A1, B, and their ratio to intracranial and extracranial atherosclerotic arterial stenosis in patients with acute ischemic stroke.

Conclusion
From the present study, it is concluded that Apo B/A1 ratio is an independent risk factor for intracranial arterial stenosis, while serum LDL cholesterol is an independent risk factor for extracranial arterial stenosis. Apo B/A1 ratio and serum LDL cholesterol are reliable serum biomarkers for cranial arterial stenosis in acute ischemic stroke patients.

Abbreviations
ELISA: Enzyme-linked immuno-sorbent assay; Apo A1: Apolipoprotein A1; Apo B: Apolipoprotein B; Apo B/A1 ratio: Apolipoprotein B/A1 ratio; ICAS: Intracranial arterial stenosis; ECAS: Extracranial arterial stenosis; WASI D: Warfarin-Aspirin Symptomatic Intracranial Disease Trial; TCD: Trans-cranial Doppler ultrasonography; MRA: Magnetic resonance angiography; MRI: Magnetic resonance imaging; CTA: Computed tomography angiography; CT: Computed tomography; VLDL: Very low-density lipoprotein; LDL: Low-density lipoprotein; LDL-C: Low-density lipoprotein-cholesterol; HDL: High-density lipoprotein; HDL-C: High-density lipoprotein-cholesterol; CCA: Common carotid artery; ICA: Internal carotid artery; PSVs: Peak systolic velocities; Met.S: Metabolic syndrome

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