TURKISH JOURNAL OF CEREBROVASCULAR DISEASES

ORIGINAL ARTICLE

Turkish Journal of Cerebrovascular Diseases 2025; 31(2):104-107
doi: 10.5505/tjcvd.2025.99267

The Role of Aortic Arch Plaques in Cryptogenic Ischemic Stroke, Detected Using Computed Tomography Angiography

Bilgisayarlı Tomografi Anjiografi Kullanılarak Tespit Edilen Aortik Ark Plaklarının Kriptojenik Iskemik Inmedeki Rolü

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ABSTRACT

Background: Various studies have shown that aortic arch plaques play a role in recurrent vascular events. In this study, we aimed to demonstrate the role of aortic arch plaques detected by Computed Tomography Angiography (CTA) in the etiology of patients followed up due to CIS.

Methods: In our retrospectively designed study, the data of 1819 ischemic stroke patients who were treated as inpatients over a two-year period were reviewed. Patients were diagnosed with CIS and CES according to the TOAST classification were included in the study. Plaques in the aortic arch were evaluated on a 3-point scale [grade 0= not present; grade 1= mild; grade 2= severe]. Detected atherosclerotic plaques were classified as non-calcified (grade 1a or 2a) or calcified (grade 1b or 2b) on a segmental basis. Additionally, plaques were divided into 4 groups according to their CT morphology: (1) Hyperdense plaques, (2) hypodense plaques, (3) a combination of both plaques, (4) ulcerated/high-risk plaques >4mm.

Results: A total of 244 patients whose data were fully available were included in the study. Among the patients,109 were female, and 135 were male, with a mean age of 69.07±13.343. Of the patients,136 had CES, and 108 had CIS. Plaques in the aortic arch were detected in 105 of the CES patients and 64 of the CIS patients. The presence of plaques was statistically significant in CES patients (P=.003). The presence of plaques was also significantly higher in older patients (P<.001). When evaluated based on plaque morphology in CTA, a statistically significant difference was found between the groups (P=.010). In the grading performed based on plaque burden, Grade1b was observed most frequently. Grade2a was not observed in any group. When considering plaque burden, there was a statistically significant difference between the two groups (P=.001).

Conclusion: Aortic arch atheroma is commonly seen in the general population. Further studies are needed to determine the role of these plaques in ischemic stroke and recurrent strokes,

Keywords: Cryptogenic ischemic stroke, aortic arch plaques, CT angiography.

ÖZ

Amaç: Çeşitli çalışmalar aort ark plaklarının tekrarlayan vasküler olaylarda rol oynadığını göstermiştir. Bu çalışmada, CIS nedeniyle takip edilen hastaların etiyolojisinde Bilgisayarlı Tomografi Anjiyografi (BTA) ile tespit edilen aort ark plaklarının rolünü göstermeyi amaçladık.

Yöntemler: Retrospektif olarak tasarlanan çalışmamızda, iki yıllık süre boyunca yatarak tedavi gören 1819 iskemik inme hastasının verileri incelendi. TOAST sınıflamasına göre CIS ve CES tanısı alan hastalar çalışmaya dahil edildi. Aort arkındaki plaklar 3 puanlı bir skala ile değerlendirildi [derece 0= yok; derece 1= hafif; derece 2= şiddetli]. Tespit edilen aterosklerotik plaklar segmental bazda kalsifiye olmayan (derece 1a veya 2a) veya kalsifiye (derece 1b veya 2b) olarak sınıflandırıldı. Ek olarak, plaklar BT morfolojilerine göre 4 gruba ayrıldı: (1) Hiperdens plaklar, (2) Hipodens plaklar, (3) Her iki plağın kombinasyonu, (4) Ülserasyonlu / yüksek riskli plaklar > 4 mm.

Bulgular: Verileri tamamen mevcut olan toplam 244 hasta çalışmaya dahil edildi. Hastaların 109'u kadın, 135'i erkekti ve yaş ortalamaları 69,07±13,343 idi. Hastaların 136'sında CES, 108'inde CIS vardı. Aort arkında plaklar CES hastalarının 105'inde ve CIS hastalarının 64'ünde tespit edildi. CES hastalarında plak varlığı istatistiksel olarak anlamlıydı (P=,003). Yaşlı hastalarda plak varlığı da anlamlı olarak daha yüksekti (P<,001). BTA'da plak morfolojisine göre değerlendirildiğinde gruplar arasında istatistiksel olarak anlamlı fark bulundu (P=,010). Plak yüküne göre yapılan derecelendirmede en sık Grade1b gözlendi. Grade2a hiçbir grupta gözlenmedi. Plak yükü dikkate alındığında iki grup arasında istatistiksel olarak anlamlı fark bulundu (P=,001).

Sonuç: Aort arkı ateromu genel popülasyonda yaygın olarak görülmektedir. Bu plakların iskemik inme ve tekrarlayan inmelerdeki rolünü belirlemek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: Kriptojenik iskemik inme, aortik ark plakları, BT anjiografi.

Cite this article as: Özaydın Göksu E, Aytekin A, Delibaş Katı Ş, Uysal E. The role of aortic arch plaques in cryptogenic ischemic stroke, detected using computed tomography angiography. *Turk J Cerebrovasc Dis.* 2025;31(2):104-107.

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Received: September 2, 2024 **Accepted:** July 24, 2025 **Publishing Date:** August 28, 2025

INTRODUCTION

Approximately 40% of cerebral infarctions lack a clearly identified cause, with embolic origins suspected in nearly 60% of these cases.[1,2] Recent research has increasingly suggested a strong association between non-stenotic aortic arch plaques and ischemic strokes, as well as subsequent vascular events.[3-5] Traditionally, transesophageal echocardiography (TEE) was the primary imaging modality for detecting aortic plaques. However, with technological advancements, computed tomography angiography (CTA) has demonstrated superior sensitivity and specificity in identifying atherosclerotic plaques.[4,6]
This study aims to evaluate the potential role of the presence and morphology of atherosclerotic plaques in the aortic arch, as detected by CTA, as a potential embolic source in patients with acute cerebral infarction of undetermined etiology, i.e., cryptogenic ischemic stroke.

MATERIAL AND METHODS

In this retrospective study, we analyzed data from 1819 ischemic stroke patients who received treatment at the Antalya Training and Research Hospital Neurology Clinic between January 1, 2020, and December 31, 2022. Patients were classified according to the TOAST classification. Those diagnosed with either cardioembolic stroke (CES) or cryptogenic stroke (CIS), whose underlying etiology remained undetermined despite extensive evaluation, were included.
Patients who underwent CTA imaging, CES patients, and CIS patients who had 24-hour Holter monitoring within the first seven days of stroke onset were included in the study (Figure 1). The CTA images of the 244 included patients were independently assessed by a blinded, experienced interventional radiologist and a neurologist, ensuring an unbiased evaluation.

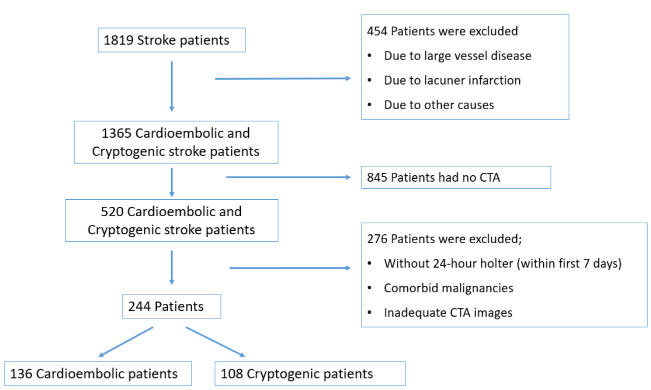

Figure 1. Study design.

MAIN POINTS

- This study aims to to evaluate the potential role of the presence and morphology of atherosclerotic plaques in the aortic arch in patients with acute cerebral infarction of undetermined etiology, i.e., cryptogenic ischemic stroke.
- Age was a significant determinant of plaque presence.
- Aortic plaques were found to be significantly more prevalent in CES patients compared with CIS patients.
- Despite the established role of plaque size and density in stroke risk, our study did not find a statistically significant correlation between plaque presence and infarct number or location (anterior/posterior/both hemispheres).

Aortic arch plaques, extending from the brachiocephalic artery to the distal segment of the left subclavian artery, were assessed using a three-tier grading system: Grade 0 (absent), Grade 1 (mild—small and infrequent plaques), and Grade 2 (severe—large and frequently occurring plaques).

A plaque is considered calcified when its radiodensity is greater than that of the intraluminal contrast agent. Conversely, a soft plaque appears hypodense on imaging due to its lipid-rich composition.
Identified atherosclerotic plaques were further classified based on their composition as either non-calcified (Grade 1a or 2a) or calcified (Some calcified plaques can be seen in the descending aorta; grade 1b, Multiple calcified plaques can be seen in the aortic arch and in the descending aorta; grade 2b). Additionally, plaque morphology was categorized into four distinct types based on CT characteristics: (1) Hyperdense plaques (hard-calcified), (2) Hypodense plaques (soft-fatty), (3) Mixed plaques (combining calcified and non-calcified components), and (4) Ulcerated/high-risk plaques (>4mm in size).
We defined ulceration as irregular edges of the plaque, similar to previous studies.[7]

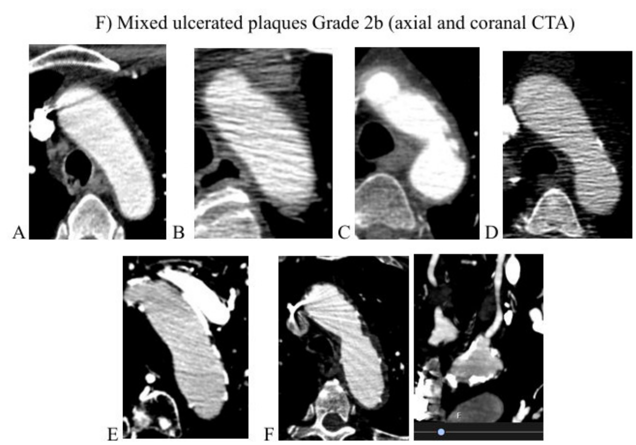

Figure 2. A: Axial CTA image showing normal aortic arch (Magnification: 600 DPI). B: Axial CTA image showing pure soft plaques (Grade 1a) (Magnification: 600 DPI). C: Axial CTA image showing pure soft and ulcerated plaques (Grade 1a) (Magnification: 600 DPI). D: Axial CTA image showing purely calcified plaque (Grade 1b) (Magnification: 600 DPI). E: Axial CTA image showing purely calcified plaque (Grade 2b) (Magnification: 600 DPI). F: Axial and coronal CTA images showing mixed ulcerated plaques (Grade 2b) (Magnification: 600 DPI).

CT Angiography Report

A CT angiography examination was performed using a Philips Brilliance 64-detector CT scanner (Philips Healthcare, 5680 DA Best, The Netherlands). Venous access was established via the antecubital vein, and 80 mL of a non-ionic contrast agent was administered at a flow rate of 4.5 mL/second. Axial-plane CT images of the carotid and cerebral arteries were acquired using a tracking method.

The acquired image slices were transferred to a Philips IntelliSpace Portal workstation (Philips Healthcare), where post-processing was performed. Multiplanar reconstructions (MPR), maximum intensity projections (MIP), and volume-rendered 3D images were generated using the AVA software.

These images, which include the aortic arch, were categorized by examining the morphology of the aortic arch plaques.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows, Version 16.0 (SPSS Inc., Chicago, IL). Continuous data were expressed as mean ± standard deviation (SD), while categorical variables were presented as percentages. Normality was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Non-normally distributed variables were analyzed using the Mann-Whitney U test, while categorical comparisons were conducted using the Chi-square or Fisher's exact test, as applicable. Statistical significance was set at P<.05.

RESULTS

Of the 244 patients included, 109 were female, and 135 were male, with a mean age of 69±13.3 years (range: 24-95). Among them, 136 patients belonged to the CES group, while 108 were in the CIS group. Aortic arch plaques were observed in 105 CES patients and 64 CIS patients, with a significantly higher prevalence in the CES group (P=.003). Advanced age was significantly associated with plaque presence (P<.001) (Table 1).

Table 1: Aortic Plaques and Their Association with Risk Factors

	Without Plaque	With Plaque	P
Age	Mean: 57,73	Mean :74,10	<.001
Under 55 years old	37	8	<.001
Over 55 years old	38	161	
Woman (n:109)	36	73	.486
Man (n:135)	39	96	.486
Hypertension (n:155)	37	118	.002
Diabetes mellitus (n:92)	25	67	.348
Coroner artery disease (n:90)	20	70	.028
Chronic kidney disease (n:5)	1	5	.106
Hyperlipidemia (n:122)	37	85	.890
Smoker (n:24)	11	13	.910
Previous stroke (n:54)	11	43	.610

A statistically significant difference was observed in the presence of plaques between the CE and CI groups (P=.03). Plaques were more frequently observed in the CE group (77.2%) compared to the cryptogenic group (59.3%).

Analysis of plaque morphology using CTA revealed notable differences between the two groups (P=.010) (Table 2).

Table 2: Plaque status according to plaque morphology in CTA

	Cardioembolic group	Cryptogenic group
Without plaque	31 (22.8%)	44 (40.7%)
Hyperdense plaque	55 (40.4%)	33 (30.6%)
Hypodense plaque	6 (4.4%)	5 (4.6%)
Mix plaque	37 (27.2%)	23 (21.3%)
High risk plaque (ulcerated/ >4mm)	7 (5.1%)	3 (2.8%)

In the grading performed based on plaque burden, Grade 1b was the most frequently observed. Grade 2a was not observed in any group. This was statistically significant between the two groups (P=.001) (Table 3).

Table 3: Grading based on plaque burden

	Cardioembolic	Cryptogenic
Absent	31 (22.8%)	44 (40.7%)
Grade 1a	2 (1.5%)	5 (4.6%)
Grade 1b	76 (55.9%)	46 (42.6%)
Grade 2a	0	0
Grade 2b	27 (19.9%)	13 (12.0%)

DISCUSSION

Our findings indicate that aortic arch plaques were present in 30.73% of patients. In our study, which focused exclusively on the aortic region due to the frequent identification of plaques in the aortic arch in previous research, plaques were observed in 77.2% of CES patients and 59.2% of CIS patients (P=.003).[7] The literature suggests considerable variability in the reported prevalence of aortic plaques in cryptogenic strokes, ranging from below 10% to over 50%, largely due to differences in imaging techniques.[8,9] Previous studies have posited a correlation between CIS and aortic atheromas, though some investigations, such as that by Petty et al., failed to establish such an association.[3-5,10]

TEE-based studies have historically provided insights into the relationship between aortic plaques and ischemic stroke. However, recent small-scale studies have highlighted CTA's superior sensitivity and specificity in detecting aortic atherosclerosis.[11-13] Despite the established role of plaque size and density in stroke risk, our study did not find a statistically significant correlation between plaque presence and infarct number or location (anterior/posterior/both hemispheres).

Recent research suggests that aortic plaques are a strong predictor of stroke and may frequently contribute to CIS.[14,15] However, contrasting findings from Kaya and Yıldız indicated a lower prevalence of aortic arch plaques in CIS and CES patients compared to other stroke categories.[7] Consistent with their results, our study also observed a reduced percentage of plaques in CIS patients

Age-related trends in aortic plaque prevalence have been well documented, with significant plaques detected in over 20% of individuals above 74 years.[16] In our study, age was a significant determinant of plaque presence. While previous research has linked aortic atheromas to hypertension, smoking, and peripheral artery disease, our findings specifically highlight significant associations with hypertension and coronary artery disease but not with other vascular risk factors.[16-18] The lower detection rate of plaques in CIS patients in our study appears to be attributed to the larger proportion of patients under 55 years old in this group. In contrast, the higher prevalence of plaques in the CES group seems to be associated with the greater number of patients over 55 years old and the presence of additional risk factors.

An autopsy study revealed that ulcerated aortic plaques were found in 60% of CIS patients and only 22% of those with clearly established stroke etiologies, emphasizing the potential role of ulceration in embolic events.[19] The variability in ulceration detection across studies likely stems from differing imaging methodologies.[20] Increased plaque thickness and complex morphological features are likely to elevate the risk of recurrent stroke.[21] High-risk plaques are typically lipid-rich, including purely soft plaques or mixed-type plaques (ulcerated and >4mm plaques). In our study, 36.05% of the plaques were found to be purely calcified (hyperdense), 4.5% were lipid-containing (hypodense), and 24.59% were mixed-type plaques. High-risk plaques (ulcerated/>4mm) accounted for 4.09% of all plaques. Both hyperdense plaques and high-risk plaques were observed more frequently in the CES group.

CONCLUSION

Plaque formation in the aortic arch is seen in 77% of cardioembolic strokes and 59.3% of cryptogenic strokes." But the frequency of "High risk plaque" is only 5.1% and 2.8%, respectively. While their contribution to stroke recurrence has been frequently reported, further research is needed to refine risk stratification and optimize secondary prevention strategies for high-risk stroke patients.

Ethics Committee Approval: Ethics committee approval was received for this retrospective study from the Clinical Research Ethics Committee of Antalya Training and Research Hospital (Date: September 7, 2023; Decision No: 12/10). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Written informed consent was not obtained from the patients due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept – E.Ö.G.; Design – E.Ö.G.; Supervision – Ş.D.K., E.U.; Resources – Ş.D.K.; Materials – E.Ö.G., A.Y.; Data Collection and/or Processing – E.Ö.G., A.Y.; Analysis and/or Interpretation – E.Ö.G., A.Y.; Literature Search – E.Ö.G., Ş.D.K.; Writing Manuscript – E.Ö.G.; Critical Review – Ş.D.K.; Other – A.Y., E.U.

Declaration of Interest: The authors have no conflicts of interest to declare.

Funding: The authors declared that this study has received no financial support.

Acknowledgments: This study was presented as an oral presentation at the 7th International Stroke Academy of Turkey and Practical Courses; November 2–5, 2023; Türkiye.

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