The association of CHA$_2$DS$_2$-VASc score and carotid plaque in patients with non-valvular atrial fibrillation

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Abstract

Objective

The aim of this study was to assess the association between CHA$_2$DS$_2$-VASc score and carotid plaques in patients with non-valvular atrial fibrillation (NVAF).

Methods

We conducted a retrospective study including 3,435 NVAF patients who underwent carotid ultrasound examinations from January 2015 to December 2017.We collected the clinical data on the medical records system. Chi-square trend test was used to analyze trends between the prevalence of carotid plaques with an increasing CHA$_2$DS$_2$-VASc score. Univariate and multivariate logistic regression was also used to assess the association between carotid plaques and CHA$_2$DS$_2$-VASc scores. The area under the receiver operating characteristic (ROC) curve (AUC) was used to determine the optimal cutoff points of different CHA$_2$DS$_2$-VASc scores in NVAF patients.

Results

NVAF patients with carotid plaques had higher CHA$_2$DS$_2$-VASc scores compared with patients who did not have carotid plaques (3.01±1.36 vs. 2.55±1.28, $P < 0.05$). In all participants, male participants and female participants, the prevalence of carotid plaques increased significantly as the CHA$_2$DS$_2$-VASc score increased (P for trend < 0.001). Multivariate logistic regression analysis demonstrated that for each 1-point increase in the CHA$_2$DS$_2$-VASc score, there was an associated 37% increase in the prevalence of carotid plaques. ROC curve analysis revealed that a CHA$_2$DS$_2$-VASc score $\geq$ 2 in male patients (sensitivity, 44.67%; specificity, 75.64%; AUC, 0.639) or $\geq$ 3 in female patients (sensitivity, 47.24%; specificity, 72.40%; AUC, 0.634) were associated with carotid plaques.

Conclusion

The prevalence of carotid plaques in patients with NVAF was associated with the CHA$_2$DS$_2$-VASc score.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia in clinical practice, and the risk of stroke in patients with AF is five-fold greater than that of non-AF[1, 2]. The CHA$_2$DS$_2$-VASc score (Congestive heart failure, Hypertension, Age $\geq$ 75 [doubled], Diabetes, Stroke [doubled], Vascular disease, Age 65 to 74, and Sex category [female]) is a simplified risk score, which contains seven clinical variables that predict stroke risk and guide anticoagulation therapy in patients with non-valvular AF (NVAF)[3].

Carotid plaque that are measured by ultrasound is a common, safe and inexpensive method for evaluating subclinical atherosclerosis owing to its shallow position and easy measurement. Recent studies have shown that addition of carotid plaque detection in the CHA$_2$DS$_2$-VASc score can better predict the occurrence of stroke in patients with NVAF[4, 5]. However, the 2016 ESC atrial fibrillation guideline does not recommend carotid ultrasound as a routine examination for patients with NVAF[6]. Moreover, routine carotid ultrasound examination for all NVAF patients would result in large medical expenses and resources consumption.

In previous studies, several components of the CHA$_2$DS$_2$-VASc score, such as advanced age, diabetes mellitus, and hypertension, have been shown to be risk factors for carotid plaque formation[7–10]. However, few studies investigated the correlation between the overall CHA$_2$DS$_2$-VASc score and carotid plaques in NVAF patients.

Therefore, we sought to design a cross-sectional study to explore the correlation between the overall CHA$_2$DS$_2$-VASc score and carotid plaques in NVAF patients. It is expected to use this well-known risk score to evaluate the presence of carotid plaque and to improve the positive rate of carotid ultrasound in NVAF patients.

Methods

Patient population

This study is a single-center, retrospective, cross-sectional study. A total of 3,435 patients with NVAF who underwent carotid ultrasound examinations due to different clinical indications in our hospital between January 2015 and December 2017 were respectively reviewed. Patients were excluded from our study if they suffered from valvular heart disease, had a history of carotid endarterectomy or carotid artery stent implantation, or suffered from significant carotid malformation. This study protocol was reviewed and approved by the Institutional Review Board of The First Affiliated Hospital of Xinjiang Medical University, and conformed to the principles and guidelines of the Declaration of Helsinki.

Data collection

All the data were acquired from electronic medical records, including demographic characteristics, lifestyle, medical history, body examination and blood laboratory tests. Age and gender were attained from the patients' Identification Card. Current smoking or drinking habits, education level and use of oral anticoagulants were determined by self-reporting. Height, weight, waist circumference (WC) and blood pressure were measured by standard and calibrated

instruments. Body mass index (BMI) was calculated as weight (in kilograms) divided by height (in meters) squared. Fasting blood glucose (FBG), triglyceride (TG), total cholesterol (TC) and low-density lipoprotein-cholesterol (LDL-C) were obtained from blood laboratory test during hospitalization. The diagnosis of diseases was from the discharge diagnosis in the medical record system and diagnostic codes were in the format of the International Classification of Disease, 9th Revision, Clinical Modification.

Assessment of carotid plaque

Carotid plaques were measured by certified and experienced sonographers using ultrasounds (Philips HD11XE ultrasound system, Philips Medical Systems, Bothell, WA). The frequency of the ultrasound probe was 7.5MHz. Both sides of the carotid arteries were extensively scanned. The patients were placed in a supine position, their heads were tilted towards the examination area, and the sonographer fully exposed one side of the neck. After checking one side, the head was turned to the opposite side and was observed in the same way. The common carotid arteries, carotid bifurcation, internal carotid artery and external carotid artery were all examined. Carotid plaques were defined as a focal structure that uplifted into the arterial lumen at least 0.5 mm or 50% of the surrounding intima-media thickness (IMT) value; or it was defined as an IMT greater than 1.5 mm. The results of carotid ultrasounds were reviewed by two independent operators and subsequently input into medical record system.

Statistical analysis

The SPSS version 22.0 software (SPSS Inc., Chicago, IL) was used to analyze the data. Continuous data were presented as means ± standard deviation (SD) and were compared by t-test analysis. Categorical data were presented as proportions and were compared with Pearson Chi-square test. The Chi-square trend test was used to analyze the trends of the detection rate of carotid plaques with an increasing CHA$_2$DS$_2$-VASc score. Univariate and multivariate logistic regression was also used to assess the association between carotid plaques and the CHA$_2$DS$_2$-VASc scores. Education level, smoking, drinking, BMI, FBG, TG, TC, and LDL-C were adjusted in the multivariate logistic regression analysis. The area under the receiver operating characteristic curve (AUC) was used to determine the optimal cutoff points of different CHA$_2$DS$_2$-VASc scores in NVAF patients. All tests were two-tailed, and a P value <0.05 was considered statistically significant.

Result

Patient characteristics

Patients were divided into two groups based on detection of a carotid plaque or not: no carotid plaque group (n = 1,632) and with carotid plaque group (n = 1,803). The characteristics and clinical data of participants, in the presence or absence of carotid plaques, are presented in Table 1. Patients with carotid plaques were older and had higher levels of SBP, DBP, FBG, TC, LDL-C, as well as a higher CHA$_2$DS$_2$-VASc score; moreover, there was a higher prevalence in males, patients with a lower education level, those who were currently smoking and drinking, as well as patients using OACs (all P value < 0.05). There was no significant difference between the two groups in WC and TG.

The prevalence of carotid plaque stratified by the CHA$_2$DS$_2$-VASc score

As shown in Fig 1, the prevalence of carotid plaques were 34.9%, 43.4%, 45.2%, 54.0%, 61.8%, 67.2%, and 71.7% in patients with a CHA$_2$DS$_2$-VASc score of 0, 1, 2, 3, 4, 5 and ≥ 6,

Table 1. Demographic and clinical data according to the detection of carotid plaques.

Characteristics	No carotid plaque	With carotid plaque	P value
	(n = 1632)	(n = 1803)	
Age, year	59.14±9.50	64.91±9.32	<0.001
Male, n (%)	505 (30.9)	806(44.7)	<0.001
Education level, n (%)			<0.001
Primary school and below	817 (50.1)	1065(59.1)	
Middle school	551 (33.8)	495(27.5)	
High school or higher	264 (16.2)	243(13.5)	
Current smoking, n (%)	247 (15.1)	342(19.0)	0.003
Current drinking, n (%)	209 (12.8)	363(20.1)	<0.001
BMI, kg/m^2	26.24±3.64	25.75±3.63	<0.001
WC, cm	88.16±11.90	88.84±11.44	0.135
SBP, mmHg	140.44±21.63	146.89±22.28	<0.001
DBP, mmHg	85.91±12.66	87.45±13.36	0.001
FBG, mmol/L	5.83±1.85	6.05±2.07	0.001
TG, mmol/L	1.70±1.17	1.74±1.09	0.290
TC, mmol/L	4.96±1.08	5.09±1.13	<0.001
LDL-C, mmol/L	2.90±0.94	2.97±0.93	0.026
OACs, n (%)	671 (41.1)	995 (55.2)	<0.001
CHA$_2$DS$_2$-VASc score	2.55±1.28	3.01±1.36	<0.001
Distribution of CHA$_2$DS$_2$-VASc score			<0.001
0 point	54 (3.3)	29 (1.6)	
1 point	273 (16.7)	209 (11.6)	
2 points	534 (32.7)	440 (24.4)	
3 points	413 (25.3)	484 (26.8)	
4 points	244 (15.0)	395 (21.9)	
5 points	88 (5.4)	180 (10.0)	
6 points or more	26 (1.6)	66 (3.7)	

BMI: body mass index, WC: waist circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, TG: triglyceride, TC: total cholesterol, LDL-C: low density lipoprotein cholesterol; OACs: oral anticoagulants.

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respectively. The prevalence of carotid plaque increased significantly with the increase of CHA$_2$DS$_2$-VASc scores in all participants, male participants and female participants (*P* for trend < 0.001).

Evaluating the cutoff value of the CHA$_2$DS$_2$-VASc score to predict carotid plaque

For male NVAF patients, a cutoff value of ≥ 2 for the CHA$_2$DS$_2$-VASc score to evaluate carotid plaques, which had a sensitivity of 44.67% and specificity of 75.64%, AUC: 0.639 with 95% CI (0.613–0.665). For female NVAF patients, a cutoff value of ≥ 3 for the CHA$_2$DS$_2$-VASc score when evaluating carotid plaque, which had a sensitivity of 47.24% and specificity of 72.40%, AUC: 0.634 with 95% CI (0.613–0.654) (Fig 2).

## Association of CHA$_2$DS$_2$-VASc score with carotid plaque

Table 2 showed that per 1-point increase in the CHA$_2$DS$_2$-VASc score, it was significantly associated with the prevalence of carotid plaque in all patients (OR: 1.304; 95% CI: 1.238–
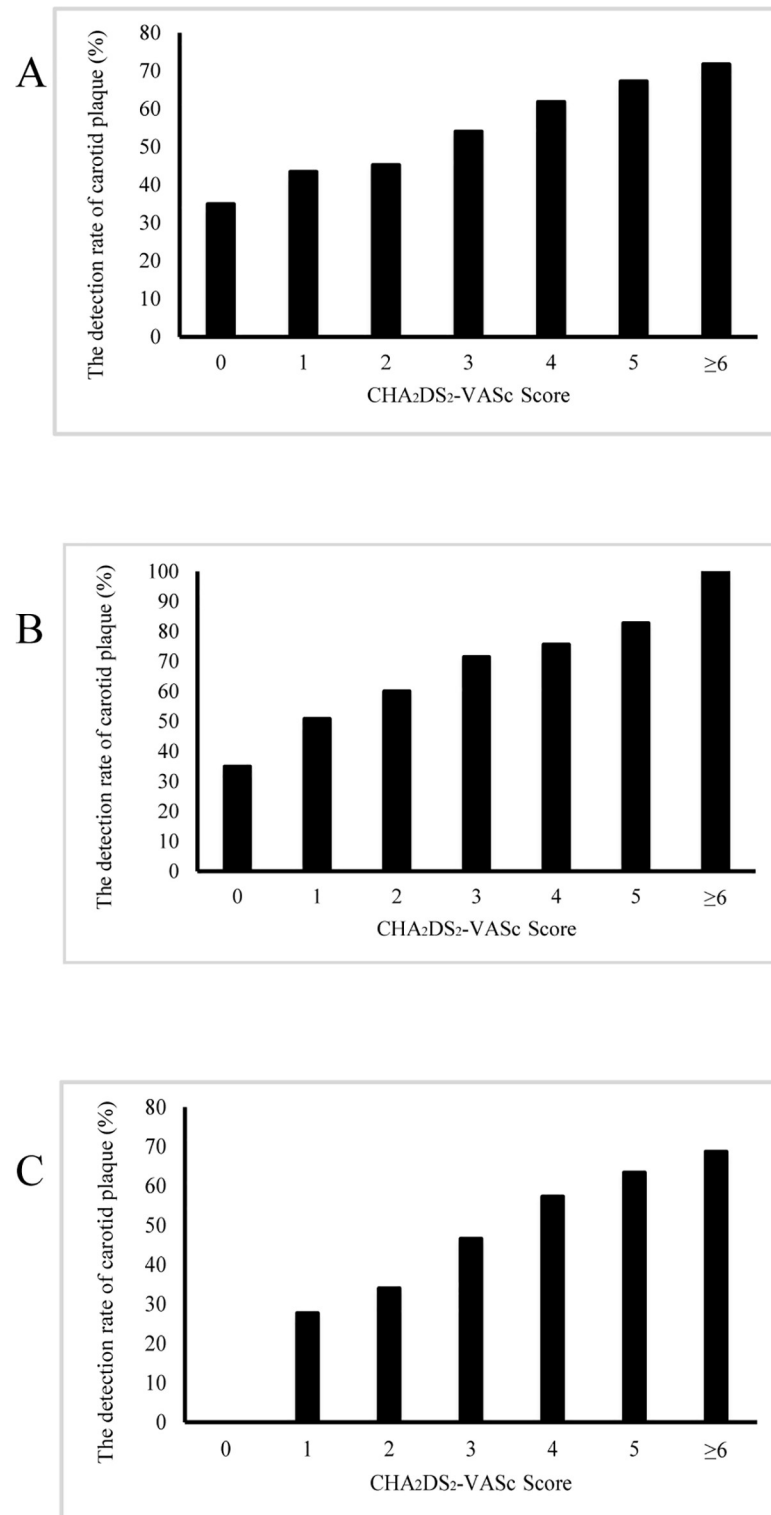
Fig 1. The prevalence of carotid plaque stratified by CHA$_2$DS$_2$-VASc score in NVAF patients. (A) In all patients (P for trend < 0.001). (B) In male patients (P for trend < 0.001). (C) In female patients (P for trend < 0.001).

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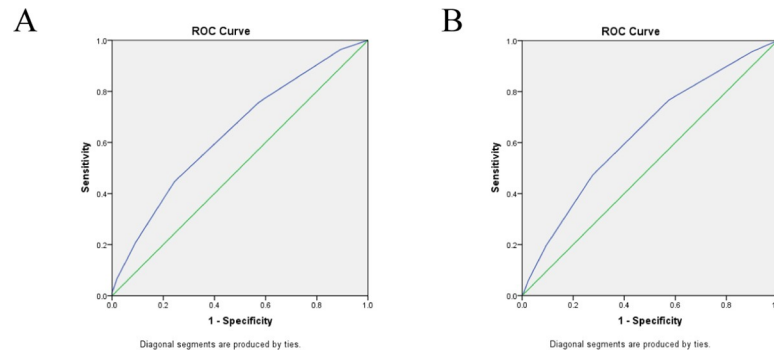
Fig 2. Receiver operating characteristic curves for CHA$_2$DS$_2$-VASc score for evaluation of carotid plaques in NVAF patients. (A) In male patients. (B) In female patients.

1.374); in male patients (OR: 1.537; 95% CI: 1.393–1.695) and in female patients (OR: 1.476; 95% CI: 1.372–1.588). Male NVAF patients who had a CHA$_2$DS$_2$-VASc score of $\geq$ 2 were 2.323-fold (95% CI: 1.829–2.950) more likely to develop carotid plaques compared with those who had a CHA$_2$DS$_2$-VASc score of $<$ 2. While female NVAF patients with a CHA$_2$DS$_2$-VASc score $\geq$ 3 were 2.437-fold (95% CI: 2.019–2.943) more likely to develop carotid plaques than those with a CHA$_2$DS$_2$-VASc score $<$ 3. In the multivariate logistic regression analysis, the CHA$_2$DS$_2$-VASc score was still a significant independent predictor of carotid plaques in both male and female NVAF patients.

Discussion

Main finding

Our key findings were as follows: (1) CHA$_2$DS$_2$-VASc score was independently associated with carotid plaques in NVAF patients; (2) The optimal cutoff point of the CHA$_2$DS$_2$-VASc score for evaluating carotid plaques were 2 and 3 in male and female NVAF patients, respectively.

Table 2. OR and 95% CI between CHA$_2$DS$_2$-VASc score and carotid plaque prevalence.

Group	Unadjusted model		Adjusted model*	
	OR (95%CI)	*P* value	OR (95%CI)	*P* value
Total study population				
Per 1-point increase	1.304 (1.238–1.374)	<0.001	1.370 (1.293–1.543)	<0.001
Male				
CHA$_2$DS$_2$-VASc score < 2	Reference		Reference	
CHA$_2$DS$_2$-VASc score ≥ 2	2.323 (1.829–2.950)	<0.001	2.429 (1.884–3.132)	<0.001
Per 1-point increase	1.537 (1.393–1.695)	<0.001	1.592 (1.431–1.770)	<0.001
Female				
CHA$_2$DS$_2$-VASc score < 3	Reference		Reference	
CHA$_2$DS$_2$-VASc score ≥ 3	2.437 (2.019–2.943)	<0.001	2.148 (1.766–2.613)	<0.001
Per 1-point increase	1.476 (1.372–1.588)	<0.001	1.410 (1.306–1.522)	<0.001

*Adjusted for education level, current smoking, current drinking, BMI, FBG, TG, TC, LDL-C.

OR: odds ratio, CI: confidence interval.

High prevalence of carotid plaque in NVAF patients

AF and atherosclerosis may influence the development of each other[11]. As a marker of sub-clinical atherosclerosis, it is supposed that NVAF patients have relatively high prevalence of carotid plaque formation[12]. However, currently there is limited data pertaining to the prevalence of carotid plaques in NVAF patients.

In a recent subgroup analysis of Atherosclerosis Risk in Communities (ARIC) study, the prevalence of carotid plaques was 38.1% in 724 patients (average age 63.3 years, female 40.1%) who developed AF within 5 years and had no history of stroke[5]. In a cohort study, to investigate the association between carotid atherosclerosis and risk of ischemic stroke in AF patients on anticoagulant treatment, the prevalence of carotid atherosclerosis was 64.7% in 587 patients (average age 74.5 years, female 41.4%)[13]. In our study, 52.5% of NVAF patients were detected with carotid plaques. The prevalence of carotid atherosclerosis is increased with age [14]. Although the average age of participants in our study was similar to those in the ARIC study, but the prevalence of carotid plaques was much higher, suggesting that the prevalence of carotid plaques in Chinese NVAF patients might be higher.

The importance of carotid ultrasound examination in NVAF patients

Stroke is the second leading cause of mortality and the third leading cause of long-term disability worldwide[15]. Furthermore, the prevention and management of ischemic stroke has become a heavy public health problem in both developed and developing countries[15, 16]. Identification of patients who are at high risk of stroke is important for providing the best treatment strategy and to improve the patients' outcome.

NVAF patients with carotid plaques have a higher stroke risk. The result of the ARIC study indicated that the presence of carotid plaques was significantly associated with a 56% increase increased stroke risk[5]. The findings from of studies conducted by Becattini et al. showed that carotid atherosclerosis was associated with a significant increase in the risk for the composite of ischemic stroke or transient ischemic attack, or death after adjusting for the CHA$_2$DS$_2$-VASc score[13]. About one-third of AF patients suffered from a non-cardioembolic stroke, the risk of ischemic stroke due to carotid atherosclerosis is underestimated in NVAF patients [17–19].

Our study suggests that the prevalence of carotid plaques increase in NVAF patients as the CHA$_2$DS$_2$-VASc score increases. For NVAF patients with a high CHA$_2$DS$_2$-VASc score, routine carotid ultrasound examinations might be recommended. Furthermore, more individualized stroke prevention strategies in NVAF patients with carotid disease should be considered.

Limitations

This study had several limitations. First, it was a single center, retrospective and observational study, and had inherent limitations of a retrospective design. Second, the study population was searched from electronic medical record system, and had selective bias. Third, the information of type of AF was lacking. Forth, some risk factors which had been verified to be related to carotid plaque were not included as the database, which might lead to some bias in multivariate logistic regression analysis. Further prospective investigations are needed to confirm this correlation.

Conclusion

In conclusion, as the CHA$_2$DS$_2$-VASC score increased, the prevalence of carotid plaques increased in NVAF patients. Carotid ultrasound examinations may be more indicated in male

NVAF patients with a CHA$_2$DS$_2$-VASc score $\geq$ 2 and female NVAF patients with a CHA$_2$DS$_2$-VASc score $\geq$ 3.

Supporting information

S1 Data.
(XLS)

S1 Text. STROBE checklist.
(DOCX)

S2 Text. Clinical studies checklist.
(DOCX)

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Writing – review & editing: Luxiang Shang, Yang Zhao, Mengjiao Shao.

References

1. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. Circulation. 1998; 98(10):946–52. Epub 1998/09/16. PMID: 9737513.

2. Wolf PA, Mitchell JB, Baker CS, Kannel WB, D'Agostino RB. Impact of atrial fibrillation on mortality, stroke, and medical costs. Archives of internal medicine. 1998; 158(3):229–34. Epub 1998/02/24. PMID: 9472202.

3. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010; 137(2):263–72. Epub 2009/09/19. https://doi.org/10.1378/chest.09-1584 PMID: 19762550.

4. Basili S, Loffredo L, Pastori D, Proietti M, Farcomeni A, Vestri AR, et al. Carotid plaque detection improves the predictive value of CHA2DS2-VASc score in patients with non-valvular atrial fibrillation: The ARAPACIS Study. International journal of cardiology. 2017; 231:143–9. Epub 2017/01/15. https://doi.org/10.1016/j.ijcard.2017.01.001 PMID: 28087176.

5. Bekwelem W, Jensen PN, Norby FL, Soliman EZ, Agarwal SK, Lip GY, et al. Carotid Atherosclerosis and Stroke in Atrial Fibrillation: The Atherosclerosis Risk in Communities Study. Stroke. 2016; 47 (6):1643–6. Epub 2016/05/25. https://doi.org/10.1161/STROKEAHA.116.013133 PMID: 27217511; PubMed Central PMCID: PMCPMC4880451.

6. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. European heart journal. 2016; 37(38):2893–962. Epub 2016/08/28. https://doi.org/10.1093/eurheartj/ehw210 PMID: 27567408.

7. Boulos NM, Gardin JM, Malik S, Postley J, Wong ND. Carotid Plaque Characterization, Stenosis, and Intima-Media Thickness According to Age and Gender in a Large Registry Cohort. The American journal of cardiology. 2016; 117(7):1185–91. Epub 2016/02/13. https://doi.org/10.1016/j.amjcard.2015.12.062 PMID: 26869392; PubMed Central PMCID: PMCPmc5371350.

8. Zhao W, Wu Y, Shi M, Bai L, Tu J, Guo Z, et al. Sex Differences in Prevalence of and Risk Factors for Carotid Plaque among Adults: A Population-based Cross-Sectional Study in Rural China. Scientific reports. 2016; 6:38618. Epub 2016/12/07. https://doi.org/10.1038/srep38618 PMID: 27922121; PubMed Central PMCID: PMCPMC5138635.

9. Wang RX, Zha J, Xu ZR. [Associations of blood pressure level with carotid intima-media thickness and plaque among middle-aged and elderly Chinese hypertensives]. Zhonghua xin xue guan bing za zhi. 2013; 41(3):256–9. Epub 2013/07/25. PMID: 23879954.

10. Sturlaugsdottir R, Aspelund T, Bjornsdottir G, Sigurdsson S, Thorsson B, Eiriksdottir G, et al. Prevalence and determinants of carotid plaque in the cross-sectional REFINE-Reykjavik study. BMJ open. 2016; 6(11):e012457. Epub 2016/11/26. https://doi.org/10.1136/bmjopen-2016-012457 PMID: 27884845; PubMed Central PMCID: PMCPMC5168519.

11. Willeit K, Kiechl S. Atherosclerosis and atrial fibrillation—two closely intertwined diseases. Atherosclerosis. 2014; 233(2):679–81. Epub 2014/02/27. https://doi.org/10.1016/j.atherosclerosis.2013.11.082 PMID: 24569021.

12. Lin LY, Yang LW, Shang YY, Li YH, Zhong M, Zhang W, et al. Role of the CHADS2 Score in the Evaluation of Carotid Atherosclerosis in Patients with Atrial Fibrillation Undergoing Carotid Artery Ultrasonography. 2018; 2018:4074286. https://doi.org/10.1155/2018/4074286 PMID: 30211222.

13. Becattini C, Dentali F, Camporese G, Sembolini A, Rancan E, Tonello C, et al. Carotid atherosclerosis and risk for ischemic stroke in patients with atrial fibrillation on oral anticoagulant treatment. Atherosclerosis. 2018; 271:177–81. Epub 2018/03/11. https://doi.org/10.1016/j.atherosclerosis.2018.02.004 PMID: 29524860.

14. Buljan K, Soldo SB, Janculjak D, Kadojic D, Candrlic M, Bensic M, et al. Relationship between Age and Thickness of Carotid Arteries in a Population without Risk Factors for Atherosclerosis. Collegium antropologicum. 2015; 39(3):779–84. Epub 2016/02/24. PMID: 26898081.

15. Feigin V, Norrving B, Mensah G. Global Burden of Stroke. Circ Res. 2017; 120(3):439–48. https://doi.org/10.1161/CIRCRESAHA.116.308413 PMID: 28154096

16. Liu L, Wang D, Wong K, Wang Y. Stroke and stroke care in China: huge burden, significant workload, and a national priority. Stroke. 2011; 42(12):3651–4. https://doi.org/10.1161/STROKEAHA.111.635755 PMID: 22052510

17. Yang P, Pak H, Park D, Yoo J, Kim T, Uhm J, et al. Non-cardioembolic risk factors in atrial fibrillation-associated ischemic stroke. PLoS ONE. 2018; 13(7):e0201062. https://doi.org/10.1371/journal.pone.0201062 PMID: 30028885

18. Arboix A, García-Eroles L, Massons J, Oliveres M, Pujades R, Targa C. Atrial fibrillation and stroke: clinical presentation of cardioembolic versus atherothrombotic infarction. Int J Cardiol. 2000; 73(1):33–42. PMID: 10748308

19. Benbir G, Uluduz D, Ince B, Bozluolcay M. Atherothrombotic ischemic stroke in patients with atrial fibrillation. Clin Neurol Neurosurg. 2007; 109(6):485–90. https://doi.org/10.1016/j.clineuro.2007.03.009 PMID: 17467891