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Original Article

Triglyceride-Related Parameters and Symptomatic Atherosclerotic Lesions in Patients With Ischemic Stroke

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ABSTRACT

Objective: Recently, evidence has suggested that the pathophysiology and risk factors of intracranial atherosclerosis (ICAS) differs from those of extracranial atherosclerosis (ECAS). In addition, novel parameters reflecting metabolic conditions, such as insulin resistance or atherogenic dyslipidemia, based on triglycerides (TG) and other biomarkers, have emerged. In this study, we evaluated the association between TG-related parameters and symptomatic cerebral atherosclerosis in patients with acute ischemic stroke resulting from large artery atherosclerosis (LAA).
Methods: We assessed consecutive acute LAA-stroke patients between January 2010 and December 2020. Based on the radiological findings, we classified the relevant symptomatic arteries that caused the index stroke into LAA-ICAS and LAA-ECAS. As TG-related parameters, the atherogenic index of plasma (AIP) and TG-glucose (TyG) index were calculated according to the following formulas: AIP = $\log_{10}$ (TG Level/High-density Lipoprotein Cholesterol Level), TyG Index = Ln (TG Level × Glucose Level/2).
Results: A total of 519 patients with LAA-stroke were evaluated. In multivariable logistic regression analysis to identify predictors of LAA-ICAS, AIP was significantly associated with LAA-ICAS (adjusted odds ratio [aOR], 3.60; 95% confidence interval [CI], 1.60–8.06). TyG index also showed a statistically significant relationship with LAA-ICAS (aOR, 1.60; 95% CI, 1.11–2.32). However, TG per se did not show a statistical association with LAA-ECAS.
Conclusion: TG-related parameters were more closely associated with stroke by ICAS than by ECAS. The metabolic conditions reflected by the AIP or TyG index, rather than hypertriglyceridemia itself, may play a greater role in determining the relevant vessel causally involved in a stroke.

Keywords: Atherosclerosis; Insulin resistance; Dyslipidemia; Triglyceride

INTRODUCTION

Cerebral atherosclerosis is a common condition found in patients with ischemic stroke and represents a major risk factor for stroke.[1,2] Strokes resulting from symptomatic atherosclerosis carry a relatively high risk of recurrence as compared to those caused by other mechanisms.[2,3] Consequently, numerous studies have been conducted to investigate the

Conflict of Interest
The authors have no conflicts of interest to declare.

Data Availability Statement
All data and materials related to this article are presented in the main text and in the supplemental materials. Data files are available from Harvard Dataverse: https://doi.org/10.7910/DVN/SWULS1.

Author Contributions
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pathological mechanisms underlying atherosclerosis development and its progression into symptomatic lesions.[4] During these investigations, low-density lipoprotein (LDL) cholesterol has garnered attention.[5] By utilizing lipid-lowering agents, such as statins, further vascular complications could be reduced by up to 20%.[5,6] However, even among patients whose LDL cholesterol levels were lowered in accordance with international guidelines, residual cardiovascular and cerebrovascular risks remained.[6,7]

Recent research has highlighted that hypertriglyceridemia and atherogenic dyslipidemia may reflect these remnant vascular risks in such individuals.[3,6] Hypertriglyceridemia has long been recognized as a major risk factor for ischemic stroke and atherosclerosis.[8] However, unlike LDL cholesterol, its clinical utility has been challenged by the variability in measured triglyceride (TG) values.[9] Nevertheless, recently, interest in novel indices, calculated from TG levels and other parameters, and that reflect meaningful pathological conditions has surged.[10,11] One such index is the atherogenic index of plasma (AIP).[10] The AIP is derived by applying the logarithmic function to the ratio of TG and high-density lipoprotein (HDL) cholesterol levels.[10] The AIP was initially proposed in 2001 as a plasma marker reflecting atherogenic dyslipidemia.[10] The AIP has also been found to exhibit a linear negative correlation with LDL particle size, making it an indirect indicator of atherogenic small dense LDL (sdLDL) particles.[10] Indeed, the AIP has been shown to be closely associated with atherosclerosis in various studies.[6,7,12] Another TG-related parameter is the triglyceride-glucose (TyG) index, which is calculated using fasting TG and glucose levels.[11] Introduced in 2008, the TyG index serves as a marker for chronic insulin resistance (IR) and has been evaluated as a reliable alternative to the homeostatic model assessment for insulin resistance (HOMA-IR).[11] Similar to the AIP, the TyG index has demonstrated a strong association with the development and progression of atherosclerosis, plaque rupture, and the prognosis of ischemic stroke.[13-17]

Intracranial and extracranial atherosclerosis (ICAS and ECAS), despite their morphological similarities, are considered distinct diseases.[18] Numerous studies have elucidated their differences in terms of structures, pathophysiology, and risk factors.[19] Even the mechanisms that lead to stroke differ between ICAS and ECAS.[18-20] These differences also appear in lipid and metabolic parameters. LDL cholesterol demonstrates a clearer association with ECAS, while triglycerides, AIP, and the TyG index exhibit a stronger link with ICAS.[3,7,14,15] However, it is important to note that most of these studies have primarily focused on the incidence or burden of asymptomatic atherosclerosis. Because most asymptomatic vessels do not play a role in the occurrence of acute stroke, it is important to focus on the symptomatic atherosclerotic lesion that caused the index stroke. Depending on the pathological mechanism of the symptomatic vessel, we will be able to predict the acute prognosis of ischemic stroke patients with large artery atherosclerosis (LAA) and provide appropriate management. Therefore, our study aimed to explore the association between TG-related parameters and the relevant symptomatic cerebral atherosclerosis in patients with acute ischemic stroke resulting from LAA. By analyzing our results, we hope to gain insights into whether hypertriglyceridemia, IR, and atherogenic dyslipidemia play a role in the process of stroke development on the atherosclerotic plaques of both intracranial and extracranial arteries.

MATERIALS AND METHODS

1. Study population

From the consecutive stroke registry of a large medical center in Korea (Seoul Metropolitan Government-Seoul National University Boramae Medical Center; SMG-SNUBMC), we included patients with acute ischemic stroke with an LAA mechanism admitted between January 2010 and December 2020. All patients admitted to our center with an acute ischemic stroke undergo extensive stroke etiology evaluation, including brain magnetic resonance imaging (MRI) and angiography (MRA), echocardiography, electrocardiography, and laboratory examination. Based on these test results, the mechanism of stroke is classified by an experienced neurologist based on Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification, and patients with stroke related to an LAA mechanism were included in this study.[21] According to the exclusion criteria, patients meeting the following conditions were excluded from the analysis:1) Age <20 years, 2) Arrival >24 hours after symptom onset, and 3) Patients without brain MRI and MRA data. Finally, 519 patients with acute LAA-stroke were included in the final analysis.

This retrospective cross-sectional study was approved by the Institutional Review Board (IRB) of SMG-SNUBMC (IRB number: 30-2022-105). The IRB waived the requirement for written informed consent because of its retrospective design and the use of de-identified information.

2. Demographic, clinical, laboratory, and radiological factors

We broadly evaluated demographic factors including age and sex, and clinical factors including hypertension, diabetes, dyslipidemia, ischemic heart disease, previous stroke, current smoking, initial stroke severity, thrombolytic therapy, use of lipid-lowering agents, LAA stroke mechanism, and systolic and diastolic blood pressure (BP). Initial stroke severity was measured by the attending physician using the National Institutes of Health Stroke Scale (NIHSS) scores. The LAA stroke mechanism was divided into the following four types by considering the size, location, number of lesions on the initial MRI diffusion-weighted imaging (DWI) image, and ICAS/ECAS on MRA images: artery-to-artery embolism, branch atheromatous disease, border-zone, and in situ thrombosis. Representative cases of each mechanism are shown in **Fig. 1**.[22]

In all study populations, laboratory examinations, including glucose profiles, lipid profiles, total white blood cell (WBC) counts, and high-sensitivity C-reactive protein (hs-CRP) levels were assessed after overnight fasting for 12 hours. The AIP was calculated by taking the $\log_{10}$ transformation of the ratio of TG and HDL cholesterol levels.[10] The TyG index was calculated according to the following formula[11]:

$$\text{TyG Index} = \text{Ln}\{\text{Fasting TG (mg/dL)} \times \text{Fasting Glucose (mg/dL)}/2\}$$

All patients underwent brain MRI and MRA within 24 hours of admission using a 1.5- or 3.0-T MR scanner (Achieva; Philips). The main outcome variable in this study was the location of the relevant symptomatic artery. Considering the following information comprehensively, we classified the relevant vessels into LAA-ICAS and LAA-ECAS, respectively: 1) Location, number of lesions, and vascular territory containing the lesion on the initial DWI image, 2) Location and stenotic degree of atherosclerotic vessel on MRA image (**Fig. 1**). There is only one relevant vessel that causes the index stroke, so all LAA-stroke patients fall into one of two groups. Therefore, we dichotomized the entire study population and defined it as a

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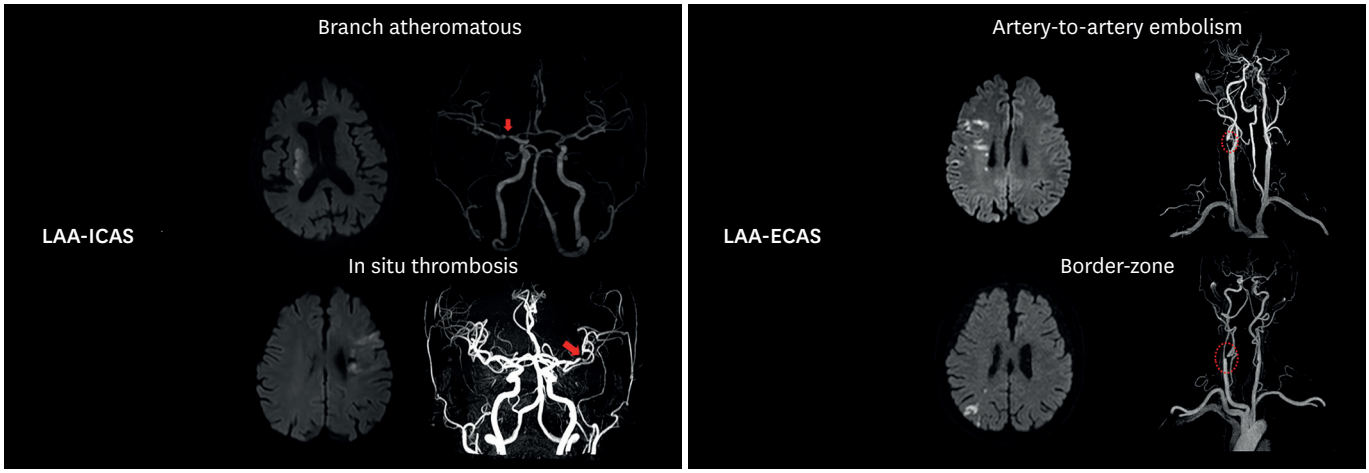

Fig. 1. Examples of representative cases according to the relevant artery and LAA-stroke mechanism investigated in this study.
(A) Single lesion, anterior perforating artery territory, right proximal MCA moderate to severe stenosis: branch atheromatous disease (LAA-ICAS group), (B) Multiple lesions, left MCA superior division territory, left M2 superior division focal severe stenosis: in situ thrombosis (LAA-ICAS group) (C) Multiple lesions, right MCA territory, right proximal ICA severe stenosis: artery-to-artery embolism (LAA-ECAS group) (D) Multiple lesions, right external border-zone area, right proximal ICA severe stenosis: border-zone (LAA-ECAS group).
LAA, large artery atherosclerosis; MCA, middle cerebral artery; ICAS, intracranial atherosclerosis; ICA, internal carotid artery; ECAS, extracranial atherosclerosis.

categorical variable. The initial classification was performed at the time of hospitalization by the attending physician who was not involved in this study and recorded in the medical record. Independently of this content, a secondary classification was made by the investigator (K.-W.N.), and in case of discrepancy between the results, the final decision was made through consultation with the third rater (H.-M.K.). If it was difficult to make a judgment in the classification process, the relevant artery was defined by referring to the patient's previous or follow-up brain images. In addition, the accompanying asymptomatic ICAS and ECAS lesions separate from the relevant vessels was classified by number into absent, single, and multiple.

3. Statistical analysis

Continuous variables with normal distributions are presented as the mean ± standard deviation, and those with a non-normal distribution as the median + interquartile range. Continuous variables with skewed data were transformed to a log scale. To analyze the difference between LAA-ICAS and LAA-ECAS, univariate analyses were conducted using the Student's *t*-test or the Mann-Whitney *U*-test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables. Those variables yielding $p<0.05$ in univariate analyses were introduced into the multivariable logistic regression analysis to evaluate the possible predictors of LAA-ICAS. Since the AIP and TyG index are variables that have significant interactions with each other due to the structures of the formula, we presented multivariable analysis using each variable individually, in the form of model 1 and model 2. Additionally, considering multicollinearity, TG-related parameters and lipid profile parameters were not included simultaneously in multivariable analyses.

Some of our study population may have had asymptomatic atherosclerotic lesions in addition to symptomatic ICAS or ECAS. As described above, in previous studies, the AIP and TyG index showed a close correlation with asymptomatic ICAS and the presence and number of lesions but did not show statistical significance for ECAS.[6,7,23] On the other hand, inflammatory markers are known to have a closer relationship with ECAS. In this study, we compared the TG-related parameters and inflammatory markers according to the number

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of lesions in ICAS or ECAS in order to verify the results of previous studies. For this, the Jonckheere-Terpstra test was used. All statistical analyses were performed using SPSS version 23.0 (IBM SPSS). All variables with a $p<0.05$ were considered statistically significant.

RESULTS

A total of 519 patients with LAA-stroke were evaluated (mean age: 69±13 years, male sex: 64.5%). The median value of the initial NIHSS score of the study population was 4 (2–7). The mean AIP value was 0.41±0.26, and the median value of the TyG index was 8.61 (8.23–9.04). When classified according to the relevant artery responsible for index stroke, 355 (68.4%) patients had LAA-ICAS, and 164 (31.6%) patients had LAA-ECAS. Other detailed baseline characteristics are presented in **Table 1**.

In the univariate analysis comparing LAA-ICAS and LAA-ECAS, LAA-ICAS was related to age, male sex, ischemic heart disease, use of lipid-lowering agents, LAA stroke mechanism, diastolic BP, total and LDL cholesterol, TG, hs-CRP, the AIP, and the TyG index (**Table 2**). In multivariable logistic analysis, the AIP was significantly related to LAA-ICAS (adjusted odds ratio [aOR], 3.60; 95% confidence interval [CI], 1.60–8.06; $p=0.002$ in model 1) after adjusting for confounders. Age, male sex, use of lipid-lowering agents, and hs-CRP were also associated with LAA-ICAS, independent of the AIP. In another multivariable analysis model using the TyG index (model 2), the TyG index showed a statistically significant association with LAA-ICAS (aOR, 1.60; 95% CI, 1.11–2.32; $p=0.012$; **Table 3**). However, TG itself did not show a statistically significant association with LAA-ECAS (**Supplementary Table 1**).

When looking at the characteristics according to the burdens of atherosclerotic lesions found in patients, the number of ICAS lesions showed a positive quantitative relationship with the AIP ($p<0.001$) and the TyG index ($p<0.001$), but no statistically significant association with hs-CRP ($p=0.214$). Conversely, the number of ECAS lesions showed a close positive quantitative relationship with hs-CRP ($p=0.017$) but showed no significant association with the AIP ($p=0.337$) and the TyG index ($p=0.399$; **Fig. 2**).

DISCUSSION

In this study, we found that TG-related parameters were more likely to induce stroke by ICAS than by ECAS. Additionally, TG itself was not able to differentiate statistically significantly between LAA-ICAS and LAA-ECAS in our data. Therefore, the metabolic conditions reflected by the AIP or the TyG index, rather than hypertriglyceridemia itself, may play a greater role in determining the relevant vessel causing a stroke.

Atherogenic dyslipidemia is a medical condition characterized by elevated TG levels, reduced HDL cholesterol levels, and the sdLDL cholesterol particles.[7,24] By including two of these three components in the formula, the AIP reflects atherogenic dyslipidemia well.[10] TG-rich lipoproteins, such as very low density lipoprotein and chylomicron, are so small that they can enter the arterial intima.[3,6] Once they enter, the TGs are cleaved by lipoprotein lipase and free fatty acids are liberated. This process results in low-grade inflammation and foam cell formation, leading to the development of atherosclerotic plaques and the occurrence of atherothrombosis.[3,6] Also, the AIP value demonstrated a linear correlation with the LDL

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Table 1. Baseline characteristics of the study population (total n=519)

Variables	Values
Demographic and clinical factors	
Age (yr)	70 (61–78)
Sex, male	335 (64.5)
Hypertension	341 (65.7)
Diabetes	167 (32.2)
Dyslipidemia	123 (23.7)
Ischemic heart disease	41 (7.9)
Current smoking	177 (34.1)
History of stroke	91 (17.5)
Initial NIHSS score	4 (2–7)
Thrombolytic therapy	42 (8.1)
Use of lipid-lowering agents	91 (17.5)
LAA stroke mechanism	
Artery-to-artery embolism	191 (36.8)
Branch atheromatous	178 (34.3)
Border-zone	90 (17.3)
In situ thrombosis	60 (11.6)
Systolic blood pressure (mmHg)	158 (141–181)
Diastolic blood pressure (mmHg)	85 (76–95)
Laboratory factors	
Hemoglobin A1c (%)	6.0 (5.6–6.9)
Fasting glucose (mg/dL)	101 (90–125)
Total cholesterol (mg/dL)	175 (151–205)
LDL cholesterol (mg/dL)	110 (85–134)
HDL cholesterol (mg/dL)	41 (35–49)
Triglyceride (mg/dL)	105 (76–147)
Total WBC ($\times 10^3/\mu L$)	7.63 (6.13–9.38)
hs-CRP (mg/dL)	0.17 (0.07–0.50)
AIP	0.41±0.26
TyG index	8.61 (8.23–9.04)
Radiological factors	
Relevant artery	
LAA-ICAS	355 (68.4)
LAA-ECAS	164 (31.6)
Numbers of intracranial atherosclerosis	
Single	186 (35.8)
Multiple	131 (25.2)
Numbers of extracranial atherosclerosis	
Single	165 (31.8)
Multiple	84 (16.2)

Continuous variables with normal distributions are presented as the mean ± standard deviation, and those with a non-normal distribution as the median (interquartile range). Data shown are number (%) not otherwise specified. NIHSS, National Institutes of Health Stroke Scale; LAA, large artery atherosclerosis; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; AIP, atherogenic index of plasma; TyG, triglyceride-glucose; ICAS, intracranial atherosclerosis; ECAS, extracranial atherosclerosis.

diameter in previous experimental studies, indirectly reflecting the sdLDL cholesterol level.[7,10,12] sdLDL particles exhibit low receptor affinity and thus have a long circulation time in the bloodstream.[12] Their small size enables easy penetration into the arterial wall, making them highly capable of inducing atherogenesis.[12] ICAS is characterized by a thinner media, less adventitia, and fewer elastic fibers than observed in ECAS.[1,3,6] As a result, the vascular wall's permeability is relatively high, allowing easy entry of various molecules into the arterial wall.[1] With aging, these vascular wall' characteristics are enhanced due to a decrease in elastic fibers and muscular components, and the accumulation of connective tissues.[1] Consequently, the difference between ICAS and ECAS becomes more pronounced in old age, which is a period when strokes often occur. Taken together, compared to ECAS, it can be concluded that ICAS has a structure more susceptible to the formation and progression of atherosclerosis

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Table 2. Baseline characteristics among groups according to the types of relevant arteries

Variables	LAA-ICAS (n=355)	LAA-ECAS (n=164)	*p*-value
Age (yr)	69 (60–77)	72 (65–79)	0.019
Male sex	204 (57.5)	131 (79.9)	<0.001
Hypertension	225 (63.4)	116 (70.7)	0.101
Diabetes	112 (31.5)	55 (33.5)	0.652
Dyslipidemia	78 (22.0)	45 (27.4)	0.173
Ischemic heart disease	22 (6.2)	19 (11.6)	0.034
Current smoking	120 (33.8)	57 (34.8)	0.831
History of stroke	61 (17.2)	30 (18.3)	0.757
Initial NIHSS score	4 (2–7)	4 (2–9)	0.357
Thrombolytic therapy	28 (7.9)	14 (8.5)	0.801
Use of lipid-lowering agents	52 (14.6)	39 (23.8)	0.011
LAA stroke mechanism			<0.001
Artery-to-artery embolism	75 (21.1)	116 (70.7)	<0.001
Branch atheromatous	178 (50.1)	0 (0.0)	<0.001
Border-zone	53 (14.9)	37 (22.6)	0.033
In situ thrombosis	49 (13.8)	11 (6.7)	0.019
Systolic BP, mmHg	162±33	160±28	0.433
Diastolic BP, mmHg	87±17	83±15	0.016
Hemoglobin A1c, %	6.0 (5.7–6.9)	6.0 (5.5–6.8)	0.337
Fasting glucose, mg/dL	101 (92–127)	99 (89–120)	0.060
Total cholesterol, mg/dL	183±44	170±41	0.001
LDL cholesterol, mg/dL	115±38	104±36	0.001
HDL cholesterol, mg/dL	41 (35–48)	42 (36–51)	0.124
Triglyceride, mg/dL	108 (77–154)	97 (75–123)	0.044
Total WBC count, x10^3/μL	7.59 (6.05–9.27)	7.70 (6.23–9.64)	0.338
hs-CRP, mg/dL	0.16 (0.06–0.45)	0.20 (0.08–0.55)	0.026
AIP	0.43±0.27	0.37±0.24	0.018
TyG index	8.69 (8.24–9.12)	8.48 (8.21–8.90)	0.006

Continuous variables with normal distributions are presented as the mean ± standard deviation, and those with a non-normal distribution as the median (interquartile range). Data shown are number (%) not otherwise specified. NIHSS, National Institutes of Health Stroke Scale; LAA, large artery atherosclerosis; ICAS, intracranial atherosclerosis; ECAS, extracranial atherosclerosis; NIHSS, National Institutes of Health Stroke Scale; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; WBC, white blood cell; hs-CRP, high-sensitivity C-reactive protein; AIP, atherogenic index of plasma; TyG, triglyceride-glucose.

Table 3. Multivariable logistic regression analysis of possible predictors of LAA-ECAS

Variables	Crude OR (95% CI)	*p*-value	Adjusted OR (95% CI)	*p*-value
Model 1				
Age	0.98 (0.97–1.00)	0.016	0.97 (0.96–0.99)	0.005
Male sex	0.34 (0.22–0.53)	<0.001	0.24 (0.15–0.39)	<0.001
Ischemic heart disease	0.50 (0.27–0.96)	0.037	0.62 (0.30–1.29)	0.203
Use of lipid-lowering agents	0.55 (0.35–0.88)	0.012	0.55 (0.32–0.92)	0.022
Diastolic BP	1.01 (1.00–1.03)	0.024	1.01 (0.99–1.02)	0.296
hs-CRP*	0.86 (0.75–0.98)	0.027	0.83 (0.72–0.96)	0.013
AIP	2.37 (1.16–4.85)	0.018	3.60 (1.60–8.06)	0.002
Model 2				
Age	0.98 (0.97–1.00)	0.016	0.98 (0.96–0.99)	0.006
Male sex	0.34 (0.22–0.53)	<0.001	0.26 (0.16–0.42)	<0.001
Ischemic heart disease	0.50 (0.27–0.96)	0.037	0.61 (0.30–1.28)	0.192
Use of lipid-lowering agents	0.55 (0.35–0.88)	0.012	0.54 (0.32–0.91)	0.021
Diastolic BP	1.01 (1.00–1.03)	0.024	1.01 (0.99–1.02)	0.341
hs-CRP*	0.86 (0.75–0.98)	0.027	0.85 (0.73–0.98)	0.023
TyG index	1.55 (1.11–2.16)	0.010	1.60 (1.11–2.32)	0.012

LAA, large artery atherosclerosis; ECAS, extracranial atherosclerosis; OR, odds ratio; CI, confidence interval; BP, blood pressure; hs-CRP, high-sensitivity C-reactive protein; AIP, atherogenic index of plasma; TyG, triglyceride-glucose.
*These variables were transformed into a log scale.

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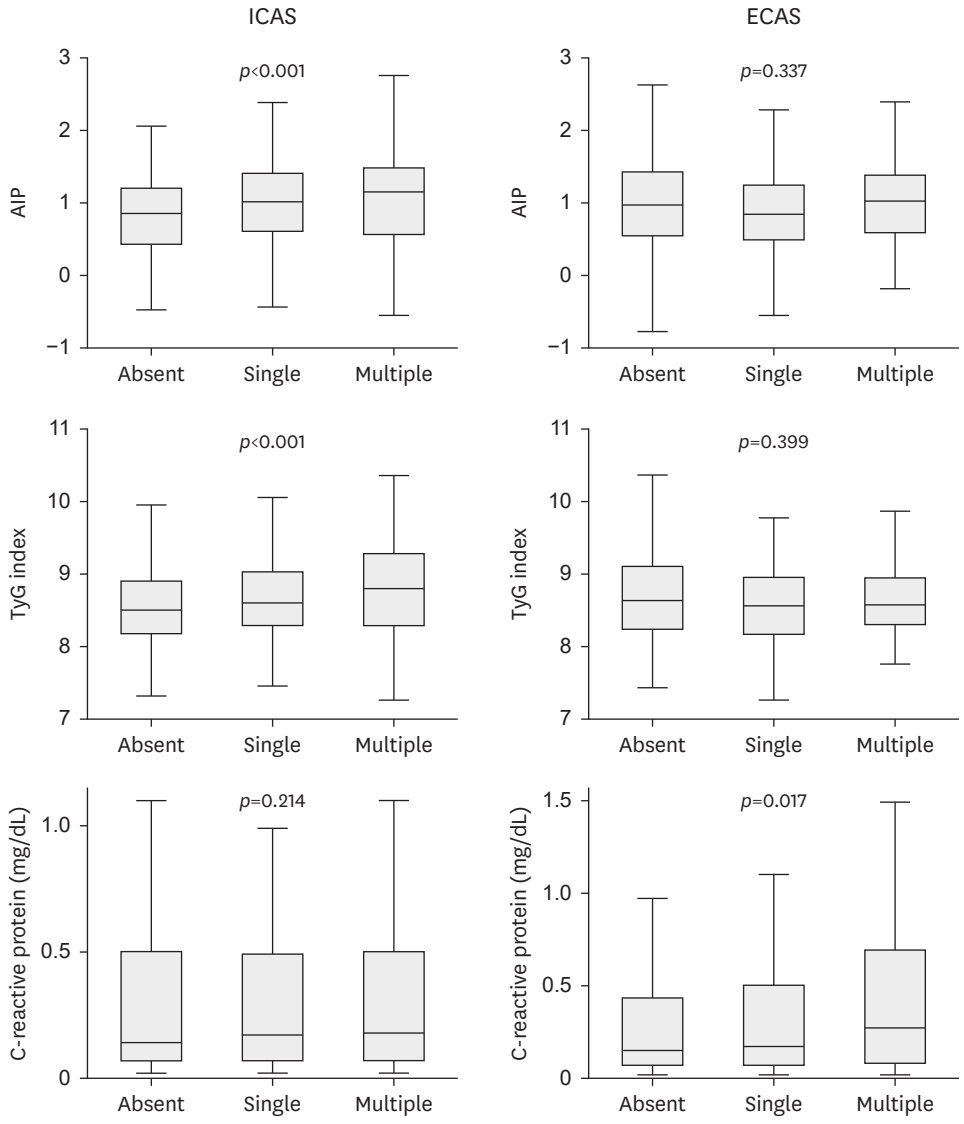

Fig. 2. Comparison of the AIP, TyG index, and hs-CRP values according to the number of ICAS and ECAS lesions.
The number of ICAS lesions showed a positive quantitative relationship with the AIP ($p<0.001$) and the TyG index ($p<0.001$), but no statistically significant association with the hs-CRP level. The number of ECAS lesions showed a strong positive quantitative relationship with hs-CRP levels ($p=0.017$), but showed no statistically significant relationship with the AIP and TyG index.
AIP, atherogenic index of plasma; TyG, triglyceride-glucose; hs-CRP, high-sensitivity C-reactive protein; ICAS, intracranial atherosclerosis; ECAS, extracranial atherosclerosis.

induced by the influx of TG-rich lipoprotein and sdLDL cholesterol (i.e., atherogenic dyslipidemia). In fact, previous studies have shown a positive correlation between TG levels and the number of asymptomatic ICAS lesions, while no statistically significant association was observed for ECAS, aortic stenosis, and coronary artery stenosis.[3,14] Our findings have additional meaning in that they show that the AIP applies even beyond the formation of simple atherosclerotic plaques to symptomatic lesions that cause stroke.

IR is a metabolic disorder in which tissue reactivity to insulin stimulation is impaired, and is usually accompanied by disorders of glucose and lipid metabolism.[25] Various studies have shown that IR is associated with the development of atherosclerosis, with plaque progression, and plaque rupture.[13,14,16,26] Thus, in our study, it was not surprising that the

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TyG index was closely related to ischemic stroke, particularly LAA-stroke. A previous study conducted by our research team had revealed a strong correlation between the TyG index and early recurrent ischemic lesions in patients with LAA stroke caused by ICAS and ECAS.[22] This association was more pronounced in cases of ICAS. Based on these results, we considered that the TyG index may be involved in the formation of symptomatic atherosclerotic lesions, which are directly involved in stroke related to ICAS rather than to ECAS, which prompted this study. In the chronic IR state, inflammation-related genes are expressed and insulin signaling is suppressed at the intimal cell level, thereby reducing the response to oxidative stress and causing chronic inflammation.[15,27] Previous experimental studies have shown that antioxidant activity is higher in ICAS than in ECAS.[1,18,20] Therefore, when antioxidant depletion conditions, such as chronic IR or reduced HDL cholesterol levels occur, ICAS may cause endothelial dysfunction and promote atherogenesis more readily than would ECAS.[1,6,7] In addition, IR reduces cerebrovascular reactivity and induces hemodynamic disturbance, which may contribute to internal border-zone infarcts in ICAS.[17] The TyG index may also reflect not only IR but may also indicate chronic hyperglycemia and atherogenic dyslipidemia.[14,23] While diabetes has previously been a risk factor for ICAS or ICAS-related stroke, association with ECAS has not been shown consistently.[28] Therefore, our results suggest that the TyG index is more closely related to ICAS, even from the perspective of hyperglycemia, is reasonable.

Someone might interpret our results as following the previous knowledge. As in previous studies,[6,9,23] LAA-ICAS showed a close association with high BP, atherogenic dyslipidemia, and IR, while LAA-ECAS showed a clear positive association with inflammatory markers, such as hs-CRP. However, our study population comprised patients with acute ischemic stroke caused by the LAA mechanism. Thus, in this study, LAA-ICAS and LAA-ECAS refer to relevant atherosclerotic lesions that caused index stroke. In other words, our results proved that the risk factors involved in generating asymptomatic ICAS or ECAS in previous studies are also closely related to the actual development of stroke from these atherosclerotic lesions.[1] In the case of ECAS, an embolic stroke occurs as plaques are ruptured by inflammation after lipid accumulation.[18,29] In support of this, our data showed that LAA-ECAS was closely associated with hs-CRP levels, and that strokes occurred mainly in the form of artery-to-artery embolism or external border-zone infarct.[30] In contrast, ICAS develops due to arteriosclerosis, in which blood vessels are stiffened by IR or metabolic disorders, and stable type atherosclerosis, in which stenosis proceeds during the healing process after silent rupture of plaque.[18,20] Consequently, relatively stable and fibrous plaques are mainly formed, and which are not thought to act as well as an embolic source.[1,18,30] This is evidenced by the fact that branch atheromatous disease or internal border-zone infarct, unrelated to plaque rupture accounted for 65% of LAA-ICAS cases. Of course, we also confirmed that the trend seen in previous studies was present in patients with LAA-stroke, by examining the association between the total number of atherosclerotic lesions and IR, atherosclerotic dyslipidemia, and inflammatory markers (**Fig. 2**).[6,18,20,23]

Several limitations should be considered when interpreting the results of this study. First, this study was a retrospective cross-sectional study using single-center data. Therefore, the observed association between the TyG index/AIP and LAA-ICAS does not imply a causal relationship. Second, since our analyses were based on a single measurement value at admission, the influence of the post-stroke hyperglycemia phenomenon during the acute period must be considered when interpreting the results of the TyG index. Third, although TG-related parameters in our study showed statistically significant differences between

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symptomatic ICAS and ECAS, the absolute value did not show much difference. Verification through follow-up studies is necessary regarding the cut-off point or usefulness of TG-related parameters to discern the location of symptomatic ICAS in actual clinical situations. Fourth, atherosclerosis is a systematic pathology, and the TG-related parameters we measured were obtained from peripheral blood. Asymptomatic ICAS and ECAS are also progressing subclinically and have the potential to cause stroke in the future, so their influence must also be considered.[31] Last, if additional test results were added to confirm the pathogenesis of LAA-stroke (e.g., transcranial Doppler, high-resolution MRA), we might be able to explain the mechanism by which the TyG index or AIP causes LAA-ICAS more clearly.

In conclusion, we found that TG-related parameters were closely related to symptomatic ICAS in patients with acute LAA-stroke. This implies that if high-risk groups among patients with asymptomatic ICAS could be identified by using the TyG index or the AIP, and they could be treated by using TG-lowering therapy, a better prognosis may be expected. Nevertheless, these hypotheses should be verified through further prospective studies.

SUPPLEMENTARY MATERIAL

Supplementary Table 1

Multivariable logistic regression analysis of possible predictors of LAA-ICAS using triglyceride as a variable

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