The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2021; 28: 776-785. http://doi.org/10.5551/jat.58339

Complex Aortic Arch Atherosclerosis in Acute Ischemic Stroke Patients with Non-Valvular Atrial Fibrillation

Masayuki Suzuki[1], Kohei Furuya[1], Misato Ozawa[1], Kumiko Miura[1], Tadashi Ozawa[1], Kosuke Matsuzono[1], Takafumi Mashiko[1], Reiji Koide[1], Shigeru Fujimoto[1] and Ryota Tanaka[1, 2]

[1]Division of Neurology, Department of Medicine, Jichi Medical University, Tochigi, Japan
[2]Stroke Center, Jichi Medical University Hospital, Tochigi, Japan

Aim: Aortic arch atherosclerosis, particularly complex aortic arch plaques (CAPs), is an important source of cerebral emboli. CAPs and atrial fibrillation (AF) often co-exist; however, the prevalence and risk of CAPs in acute ischemic stroke patients with AF is unclear.

Methods: In patients with acute ischemic stroke with non-valvular AF admitted to Jichi Medical University Hospital during April 2016 to September 2019, we retrospectively evaluated the presence of CAPs on transesophageal echocardiography (TEE).

Results: CAPs were observed in 41 (38.7 %) of 106 patients with non-valvular AF. Older age, diabetes mellitus, chronic kidney disease, low high-density lipoprotein cholesterol (HDL-C) levels, higher levels of glycohemoglobin A1c (HbA1c), higher $CHADS_2$ and CHA_2DS_2-VASc scores, and intracranial or carotid artery stenosis were more frequently observed in CAPs-positive than in CAPs-negative patients. In multivariable analyses, older age (odds ratio [OR]: 1.2 per year increase; 95% confidence interval [CI]: 1.07–1.24; $P<0.0001$), diabetes mellitus (OR: 4.7; 95%CI: 1.27-17.35; $P<0.05$), and low HDL-C (OR: 0.95 per 1 mg/dl increase; 95%CI: 0.92-0.99; $P<0.01$) were independent risk factors for CAPs. The prevalence of CAPs was age-dependent, and there was a significantly higher risk in patients aged either 75–84 years or >84 years than in those aged <65 (OR: 7.6; 95%CI: 1.50-38.62, and OR: 32.1; 95%CI: 5.14-200.11, respectively).

Conclusions: Even in patients with ischemic stroke with non-valvular AF, concomitant CAPs should be considered in older individuals and those who have diabetes or low HDL-C.

See correspondene vol. 28: 786-788

Key words: Acute stroke, Complex aortic arch plaque, Non-valvular atrial fibrillation, Diabetes mellitus, Low HDL-C

1. Introduction

Aortic arch atherosclerosis is an important source of embolic stroke. Transesophageal echocardiography (TEE) facilitates detection of aortic arch plaques and diagnosis of aortogenic embolic stroke[1, 2]. Complex aortic arch plaques (CAPs), detected by TEE, and defined as large plaques (≥ 4 mm in thickness), plaques with ulceration, and plaques with a mobile component correlate with an increased clinical risk of stroke[3]. Additionally, in patients with embolic stroke of undetermined source (ESUS), large aortic arch plaques or CAPs are thought to be an important source of embolism and are associated with stroke recurrence[4, 5].

The burden of atrial fibrillation (AF) increases with aging in the general population; this is relevant to both cardiovascular and ischemic stroke[6, 7]. A previous study showed that aortic arch plaques are also found in patients with AF, and the presence of CAPs was associated with atherosclerotic risk factors and left atrial stasis or thrombosis[8]. Although CAPs is an

Address for correspondence: Ryota Tanaka, Stroke Center, Jichi Medical University Hospital, and Division of Neurology, Department of Medicine, Jichi Medical University, 3311-1, Yakushiji, Shimotsuke city, Tochigi, 329-0498, Japan E-mail: rtanaka@jichi.ac.jp

Received: June 5, 2020 Accepted for publication: July 31, 2020

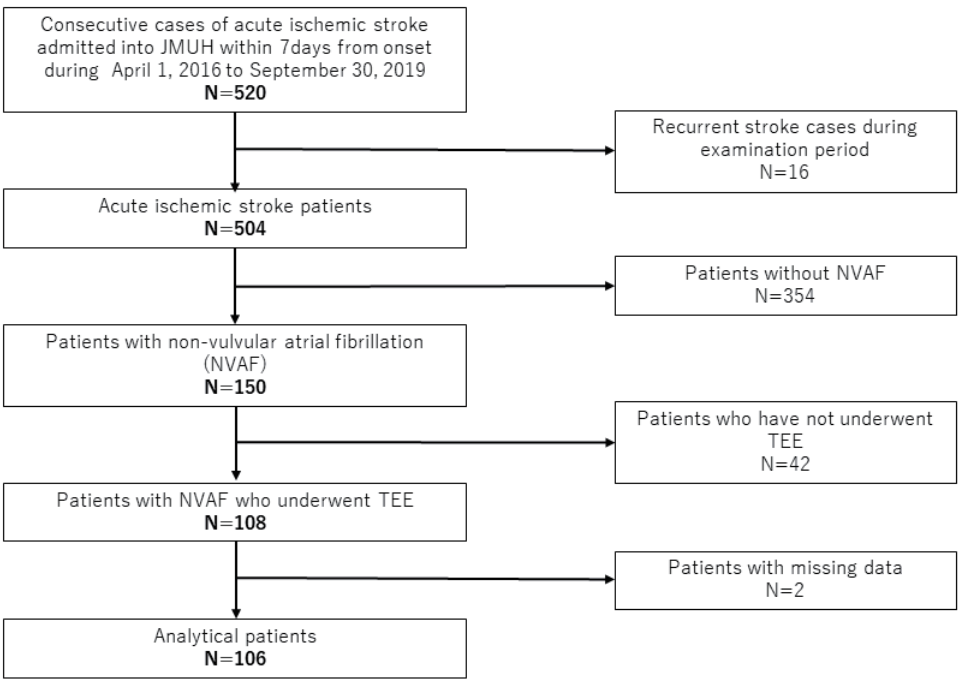

Fig. 1. Flow diagram of patient enrollment in the present study

important embolic source for ischemic stroke, its prevalence has not yet been systematically evaluated in patients with acute ischemic stroke with non-valvular AF. Thus, we here investigated the prevalence of CAPs in patients with acute ischemic stroke with non-valvular AF and the predictors thereof.

2. Methods

2.1. Study Design and Protocol

This study was performed retrospectively with the data from the stroke data-base of a single stroke center in Jichi Medical University Hospital, Tochigi, Japan. We enrolled patients who were admitted to the Division of Neurology, Department of Medicine, Jichi Medical University Hospital, with a diagnosis of the acute ischemic stroke, within 7 days from the onset, between April 2016 and September 2019. Among the 520 cases with acute ischemic stroke, 16 cases were excluded due to recurrence during the study period, and 354 cases were excluded due to a lack of evidence of AF. Among the remaining 150, 42 cases were excluded due to lack of TEE data, and two cases were excluded due to other missing data **(Fig. 1)**. Confirmation of non-valvular AF was based on ECG findings on admission or in past medical records. Patients whose AF was newly detected on the hospital ward electrocardiogram monitor or 24 hour-Holter electrocardiogram during hospitalization were also included. If the initially detected AF episodes terminated spontaneously within 7 days, or those recurred, they were diagnosed as paroxysmal AF. Other AF, with episodes lasting longer than 7 days, were diagnosed as chronic AF. The diagnosis of acute ischemic stroke was defined by the presence of a focal neurological deficit and with corresponding lesion confirmed by a high signal on diffusion-weighted images (DWI). Transient ischemic attack (TIA), which defined as transient neurological deficits caused by focal brain or retinal ischemia, was excluded in this study. All patients were assessed using the National Institutes of Health Stroke Scale (NIHSS) at admission.

Baseline clinical data were obtained from medical records; these included age, sex, body mass index (BMI), patient's smoking and drinking habits, and vascular risk factors. Medical history such as symptomatic ischemic stroke, coronary artery disease (angina pectoris and myocardial infarction), and peripheral artery disease was also analyzed. The pre-stroke $CHADS_2$ or CHA_2DS_2-VASc score were also calculated. Pre-stroke use of medication, such as antiplatelet medication, anticoagulation (warfarin or direct oral anticoagulation), and statin was also confirmed. Blood samples were collected at admission. Written informed consent was obtained from all participants in this study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and the study protocol was approved by the ethics committee of Jichi Medical University Hospital.

2.2. Brain Magnetic Resonance Imaging and Magnetic Resonance Angiography

Brain magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) were performed by using a 1.5-T or 3-T MR system (MAGNETOM Avanto, MAGNETOM Skyra, MAGNETOM Symphony; Siemens, Munich, Germany) for all patients enrolled. The whole brain was scanned at a slice thickness of 5 mm with an interslice gap of 1.5 mm; 22 axial images were obtained. Stenosis of the major intracranial arteries, including the middle cerebral artery (MCA), internal carotid artery (ICA), vertebral artery, and basilar artery was defined as >50% narrowing of the artery on MRA, based on the WASID measurement criteria[9].

2.3. Carotid Echosonography

Carotid echosonography was performed using a commercially available ultrasound imaging system (ProSound α7, Hitachi Aloka Medical, EPIQ7; Philips, Best, The Netherlands) by a neurologist on admission. Carotid stenosis was evaluated in terms of area stenosis and was defined as >50% narrowing in the lumen of the carotid artery, including the common carotid artery, bifurcation, and internal carotid artery.

2.4. Transesophageal Echocardiography

TEE was performed using a commercially available ultrasound imaging system (EPIQ7; Philips) with the use of a multiplane TEE probe. In TEE, before evaluating the aortic plaques, the presence of the thrombus and the density of spontaneous echo contrast within the left atrium (LA) and LA appendage (LAA), LAA flow velocity, atrial septum aneurysm, and valvular disease of the aortic and mitral valves were assessed. Then, by withdrawing the TEE probe, we observed the aortic plaques from the descending aorta to the aortic arch.

We evaluated the maximum thickness, and characteristics of the plaques at the aortic arch, such as the presence of a mobile component or ulceration. Ulceration was defined as formation of a recess with a depth >2 mm from the luminal surface of the plaque and with a base width >2 mm. Complex aortic arch plaques (CAPs) were defined as large plaques (≥ 4 mm in thickness), plaques with ulceration, or plaques with mobile components[10]. TEE was performed by a neurologist and the findings were confirmed by multiple neurologists.

2.5. Clinical Variables

We collected the following clinical variables for each patient: age; sex; BMI, smoking status; the type of AF; past ischemic stroke or cardiovascular disease; hypertension; dyslipidemia; diabetes mellitus; peripheral artery disease; estimated glomerular filtration rate (eGFR); hemodialysis; medication before onset (such as anticoagulant, antiplatelet or statin); NIHSS score on admission; pre-stroke low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride; blood glucose; glycohemoglobin A1c (HbA1c); and brain natriuretic peptide levels on blood test at admission. Hypertension was defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg, or a history of using antihypertensive medications. Diabetes mellitus was determined by the presence of an existing diagnosis with use of glucose-lowering medication, a fasting blood glucose level ≥ 126 mg/dL, a casual blood glucose level ≥ 200 mg/dL, an HbA1c level ≥ 6.5%, or newly diagnosed as a glucose level ≥ 200 mg/dL at 2 hours after a 75g oral glucose tolerance test. Dyslipidemia was defined as an LDL-C ≥ 140 mg/dL, an HDL-C value ≤ 40 mg/dL, or the use of cholesterol-lowering medication.

2.6. Statistical Analysis

Continuous variables were compared with either Student's *t*-test or one-way analysis of variance with Dunnett's multiple comparison post hoc test. The frequency of categorical variables was compared with χ^2 test. We performed multivariate logistic regression analyses to evaluate the association of CAPs and several potential risk factors. Clinical variables that were significant following univariate analysis were included. Statistical analyses were performed using the JMP Version 14.2 software program (SAS Institute Inc., Cary, NC, USA). A value of $P<0.05$ was considered to indicate statistical significance.

3. Results

3.1. Baseline Characteristics of CAPs-Positive Nonvalvular Atrial Fibrillation

We identified 106 consecutive patients with nonvalvular AF who underwent TEE. The baseline characteristics of those 106 patients and those who did not undergo TEE are compared in **Supplementary Table 1**. Of these 106 patients, 41 (38.7%) were CAPs-positive by TEE. The characteristics of these 106 patients are listed in **Table 1**, according to the presence or absence of CAPs. No significant differences were noted between CAPs-positive and CAPs-negative patients in terms of sex, BMI, hypertension, dyslipidemia, smoking status, history of stroke or cardiovascular disease, and pre-stroke anti-thrombotic medication. However, the CAPs-positive group was significantly older (80.2 ± 8.2 years vs 72.7 ± 9.0 years; $P<$

Table 1. Comparison of clinical and demographic features of patients according to the presence of CAPs

	CAPs (-)	CAPs (+)	*P*
N=106	65	41 (38.7%)	
Age	72.7±9.0	80.2±8.2	<0.0001
SEX (F)	19 (29.2%)	13 (31.7%)	0.79
Body mass index	23.1±3.8	22.6±2.7	0.41
Hypertension	51 (78.5%)	38 (92.7%)	0.052
Dyslipidemia	27 (41.5%)	21 (51.2%)	0.33
Diabetes mellitus	17 (26.2%)	21 (51.2%)	<0.01
Chronic kidney disease	26 (40%)	27 (65.9%)	<0.01
Hemodialysis	1 (1.5%)	2 (4.9%)	0.31
Chronic atrial fibrillation	22 (33.9%)	21 (51.2%)	0.08
Paroxysmal atrial fibrillation	43 (66.2%)	20 (48.8%)	0.08
Chronic heart failure	16 (24.6%)	7 (17.1%)	0.36
Current smoke	11 (16.9%)	7 (17.5%)	0.94
Medical history			
Ischemic stroke	12 (18.5%)	13 (31.7%)	0.12
Coronary artery disease	5 (7.7%)	7 (17.1%)	0.14
Peripheral artery disease	1 (1.5%)	4 (9.8%)	0.052
$CHADS_2$ score	2 (0-6)	3 (0-5)	<0.001
CHA_2DS_2-VASc score	3 (0-8)	4 (1-7)	<0.001
Prestroke med			
Antiplatelet therapy	9 (13.9%)	11 (26.8%)	0.1
Oral anticoagulation	28 (43.1%)	13 (31.2%)	0.24
Warfarin	14 (21.5%)	4 (9.8%)	0.12
Direct oral anticoagulation	12 (18.5%)	5 (12.2%)	0.39
Statin	11 (16.9%)	12 (29.3%)	0.13
Data			
LDL-C (mg/dl)	108.8±33.1	114.5±35.8	0.41
HDL-C (mg/dl)	60.3±15.7	50±15.3	<0.01
TG (mg/dl)	113.4±93.8	119.8±69.9	0.71
BS (mg/dl)	134.2±41.7	140.4±39.4	0.44
HbA1c (%)	6.1±0.97	6.5±1.2	<0.05
BNP (pg/dl)	214.3±316.5	231.6±235.6	0.76
Clinical and imaging data			
NIHSS	10.4±9.9	10.9±9.3	0.82
Intracranial artery stenosis	5 (7.7%)	11 (26.8%)	<0.01
Carotid artery stenosis	5 (7.7%)	9 (22%)	<0.05
Multiple infarcts on DWI	32 (51.6%)	22 (53.7%)	0.84
Cortical infarcts on DWI	46 (74.2%)	31 (75.6%)	0.87
Multi-vascular territory infarcts on DWI	6 (9.7%)	4 (10%)	0.96

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; BS, blood sugar; HbA1c, glycohemoglobin A1c; BNP, brain natriuretic peptide; NIHSS, National Institutes of Health Stroke Scale score; DWI, diffusion-weighted image; NS, non-significant

0.0001) and had a significantly higher prevalence of diabetes mellitus (51.2% vs 26.2%; $P<0.01$), chronic kidney disease (CKD; 65.9% vs 40.0%; $P<0.01$). The $CHADS_2$ and CHA_2DS_2-VASc scores before the index event were also higher in the CAPs-positive group (3 [0–5] vs 2 [0–6] for $CHADS_2$, 4 [1–7] vs 3 [0–8] for CHA_2DS_2-VASc, $P<0.001$). HDL-C (50.0±15.3 vs 60.3±15.7; $P<0.01$) and HbA1c (6.5±1.2 vs 6.1±0.9, $P<0.05$) levels differed significantly, and the prevalence of intracranial and carotid artery stenosis was significantly higher in the CAPs-positive than in the CAPs-negative group (26.8% vs 7.7% for intracranial stenosis, $P<0.01$, 22.0% vs 7.7%, for carotid artery stenosis, $P<0.05$). However,

Table 2. Association between vascular risk factors and presence of CAPs in NVAF

	Univariate			Multivariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Age (per years increase)	1.1	1.05-1.16	<0.0001	1.2	1.07-1.24	<0.0001
Diabetes mellitus	3.0	1.30-6.77	<0.001	4.7	1.27-17.35	<0.05
Chronic kidney disease	3.0	1.28-6.53	<0.05	1.6	0.57-4.76	0.36
HDL-C (per 1mg/dL increase)	0.96	0.93-0.98	<0.01	0.95	0.92-0.99	<0.01
HbA1c	1.5	0.99-2.11	0.052			
$CHADS_2$ score	1.7	1.20-2.33	<0.01	1.5	0.60-3.92	0.37
CHA_2DS_2-VASc score	1.5	1.16-1.93	<0.01	0.7	0.31-1.43	0.29
Intracranial artery stenosis	4.4	1.40-13.82	<0.05	1.9	0.45-8.08	0.38
Carotid artery stenosis	3.4	1.04-10.92	<0.05	4.5	0.97-20.50	0.055

HDL-C, high-density lipoprotein cholesterol; HbA1c, glycohemoglobin A1c; CAPs, complex aortic arch plaques; NVAF, non-valvular atrial fibrillation

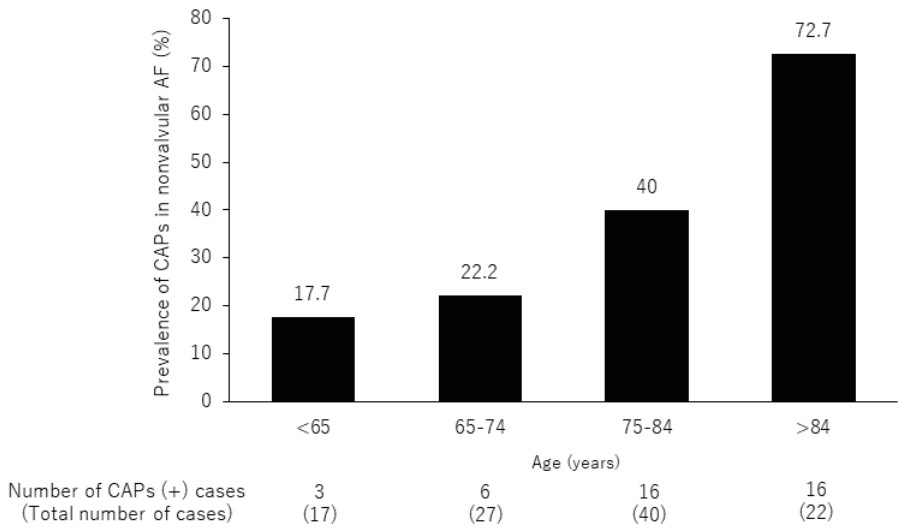

Fig. 2. Age dependent prevalence of complex aortic arch plaque (CAPs)
There is a significant age-dependent increase in the prevalence of CAPs ($P<0.001$).

we did not find any differences in the imaging patterns of DWI, such as single or multiple infarcts, cortical infarcts, and multiple-vascular territory infarcts.

3.2. Association between Vascular Risk Factors and Presence of CAPs in Patients with Non-valvular AF

The univariate odds ratios (ORs) for the presence of CAPs in patients with acute ischemic stroke with non-valvular AF were significant for age, diabetes, CKD, HDL-C, $CHADS_2$ and CHA_2DS_2-VASc scores, intracranial artery stenosis, and carotid artery stenosis (Table 2). Multivariate logistic regression analysis showed that independent risk factors for the presence of CAPs were age (OR: 1.2 per year increase, 95%CI: 1.07–1.24, $P<0.0001$), diabetes (OR: 4.7, 95% CI 1.27 – 17.35, $P<0.05$), and HDL-C (OR: 0.96 per 1 mg/dl increase, 95%CI: 0.92–0.99, $P<0.01$) (Table 2).

3.3. Age-Dependent Prevalence of CAPs

Age was significantly associated with the presence of CAPs in acute ischemic stroke patients; subsequently we divided the prevalence of CAPs according to four age categories: age <65, 65–74, 75–84, and >84 years. The prevalence of CAPs in these categories was 17.7%, 22.2%, 40.0%, and 72.7%, respectively (Fig. 2). However, there was no association between age and other risk factors of CAPs, such as diabetes, CKD, HDL-C, HbA1c, or intra-and extra-cranial artery stenosis (data not shown). The risk of CAPs being present was significantly higher for patients aged >84 years than those aged <65 years (Table 3; OR:

Table 3. Age-dependent risk of CAPs in patients with acute ischemic stroke with non-valvular AF

	Univariate			Multivariate		
Age	OR	95% CI	*P* value	OR	95% CI	*P* value
<65 years	1.0	-	-	1.0	-	-
65-74 years	1.3	0.29-6.23	0.71	3.0	0.52-16.92	0.22
75-84 years	3.1	0.77-12.59	0.11	7.6	1.50-38.62	<0.05
>84 years	12.4	2.61-59.3	<0.01	32.1	5.14-200.11	<0.001

CAPs, complex aortic arch plaques; AF, atrial fibrillation; OR, odds ratio; CI, confidence interval, multivariate regression analysis was performed adjusting for diabetes and HDL-C level

12.4, 95%CI: 2.6-59.3, $P<0.01$). The same trend was observed for the 75–84 year and >84 year age groups, after adjusting for diabetes and HDL-C level (**Table 3**; OR: 7.6, 95%CI 1.50–38.62, $P<0.05$; and OR: 32.1, 95% CI 5.14–200.11, $P<0.001$, respectively).

4. Discussion

Although aortic arch atherosclerosis and atrial fibrillation often co-exist, little is known about the prevalence and risk factors for aortic arch atherosclerosis in acute ischemic stroke patients with AF. In our retrospective study of patients with acute ischemic stroke who also had non-valvular AF, we found that almost 40% of these patients had CAPs, indicating an additional embolus source. Moreover, we found that the risk of having CAPs was higher in older patients, in those who had low HDL-C levels, or who had diabetes mellitus.

The prevalence of atherosclerotic aortic plaques with a complex component, evaluated by TEE, has been reported to be 8.3–25% in patients with non-valvular AF[8, 11-13]. The prevalence of CAPs tends to be higher in American than in the East Asian populations with non-valvular AF (25% vs 8.3–19%, respectively). These studies included a low number of patients with non-valvular AF who had a previous history of thromboembolism including stroke and TIA (14.8–22.2 %); however, there have been few studies of the presence of CAPs in patients with acute ischemic stroke accompanying AF. Among patients with acute stroke and TIA, the prevalence of CAPs was more frequent (14–39.3%)[14-16]. Kitano *et al.* reported that the prevalence of CAPs was 39.3% in cases of acute ischemic stroke[15]. In their study, CAPs were found in 13.6% of cases with cardioembolic stroke, but in 55.6% of those with other causes of stroke. Because the decision about whether to perform TEE in those studies was made by each physician according to the necessity of searching for the embolic source, the overall prevalence of CAPs in acute ischemic stroke remains unclear. Accordingly, recent studies that have analyzed patients with ESUS showed that the prevalence of CAPs was also higher in these patients (29–38%)[4, 5]. Our data showed that the prevalence of CAPs was 38.7% in consecutive hospitalized patients with acute ischemic stroke who also had non-valvular AF.

As the mean age of all enrolled patients was 75.5±9.3 years and that of the CAPs-positive group was 80.2±8.2 years, the higher prevalence of CAPs in this cohort may be related to their higher age. A previous study also demonstrated that the prevalence of aortic arch atheroma increased according to age[1], and our results showed that the prevalence of CAPs, particularly for those aged >75 years, was significantly higher than that for those aged <65 years among patients with non-valvular AF. Thus, there is an increased need for paying special attention to elderly stroke patients with non-valvular AF, as they may have another source of stroke-causing emboli.

Diabetes mellitus was also an independent predictor of CAPs in our study, as supported by previous studies. Diabetes mellitus has been shown to increase atherosclerosis by multi-pathological mechanisms, such as oxidative stress, increased inflammation, and vasa vasorum neovascularization[17]; it was associated with the plaque burden, a greater necrotic core size, and inflammation characterized by infiltration of macrophages and T cells in patients with coronary artery disease[18]. In the carotid artery, high-risk, unstable plaques evaluated on MRI plaque images were more prevalent in patients with diabetes who had moderate to high-grade internal carotid artery stenosis[19]. Further, MRI based plaque imaging showed that type 2 diabetes was significantly associated with the presence of vulnerable carotid plaques, independent of the degree of stenosis[19]. Another study showed that the presence of diabetes was an independent risk factor for vulnerable aortic plaque burden, as evaluated by aortic angioscopy[20]. They evaluated the presence of aortic plaques and the distribution of plaque instability in patients with coronary artery disease, and found that diabetes mellitus and peripheral arterial disease were

significantly associated with vulnerable plaques, such as intense yellow plaques, ruptured plaques, and thrombi[20]. Taken together with our results, these data suggest that diabetes mellitus is an important predictor of aortic arch atherosclerosis in patients with acute ischemic stroke who have AF.

Epidemiological studies have shown that plasma HDL-C levels are inversely correlated with atherosclerotic cardiovascular disease; however, a more recent analysis has questioned this association[21]. Several anti-atherosclerotic functions of HDL-C have been proposed, such as removal of cholesterol from macrophages within the arterial wall and its delivery to the liver for excretion, endothelial protection by inhibiting the production of cell-adhesion and pro-inflammatory molecules, and anti-oxidant activity[22]. These proposals may explain the reverse association between HDL-C and CAPs found in this study.

The prognosis of these patients, as well as effective treatment, remains unclear. Okura *et al.* reported an association between aortic atherosclerotic plaque (AoP) and long-term prognosis in patients with AF[11], based on a study of 108 consecutive patients with AF who underwent TEE, including 21 patients (19%) with AoP ≥ 4 mm and 24 patients (22.2%) with previous stroke. The frequency of cardiovascular events, including ischemic stroke, was significantly higher in patients with AoP ≥ 4 mm than in those with AoP < 4 mm, and AoP ≥ 4 mm was an independent predictor of cardiovascular events (relative risk [RR]: 2.86, 95%CI 1.23–6.65, $P=0.02$). Another study demonstrated predictors of the presence of silent brain infarction in patients with non-valvular AF who underwent transcatheter AF ablation[12]. An evaluation performed before transcatheter ablation showed that 30% of patients had silent brain infarction; 84% involved small-diameter lesions (< 15 mm) and 61% had multiple lesions. CAPs were an independent predictor of silent brain infarctions (OR: 4.82, 95%CI 1.23–18.92, $P=0.024$), as were age and a $CHADS_2$ score ≥ 2, and LA abnormalities, such as LA thrombus, SEC, and LAA emptying velocity. These data suggested that vulnerable aortic arch atherosclerosis is another important source of emboli in patients with non-valvular AF.

Oral anticoagulants (OAC) should be introduced as a secondary prevention in patients with acute ischemic stroke with non-valvular AF; however, there is no evidence to date on whether dual antithrombotic therapy is superior to a single oral anticoagulant for patients with non-valvular AF and CAPs. A previous study has shown that the risk of major bleeding complication was significantly higher in patients treated with dual antithrombotic medication (warfarin plus antiplatelet) than those treated with warfarin monotherapy for stroke and cardiovascular disease[23]. Subanalyses of large clinical trials of four novel oral anticoagulants (NOAC) showed taking antiplatelet for any reason with OAC had no apparent benefit in preventing cardiovascular event, and also increased the risk of major bleeding[24-27]. The Fushimi AF registry demonstrated that major bleeding occurred more frequently in patients with atrial fibrillation administered a combination therapy (OAC plus antiplatelet) than in those administered OAC alone; cardiovascular events also occurred more frequently in the combination therapy group than in the OAC alone group[28]. A recent study reported that the efficacy and safety of rivaroxaban monotherapy was noninferior and superior, respectively, to combination therapy (rivaroxaban plus antiplatelet) in patients with atrial fibrillation and stable coronary artery disease[29]. These data suggest that long-term dual antithrombotic therapy may not only increase the risk of bleeding complication, but have no benefit regarding cardiovascular events in patients with AF. Therefore, further study is warranted to confirm the optimal antithrombotic medication for secondary prevention in patients with non-valvular AF and CAPs.

Lipid control is also important target for the secondary prevention of ischemic stroke. The SPARCL trial demonstrated that treatment with 80 mg atorvastatin per day resulted in a 16% relative risk reduction of stroke recurrence compared with placebo in patients with stroke and TIA[30]. The American and European guidelines both recommend intensive lipid lowering therapy using statins after TIA or ischemic stroke with atherosclerotic origin[31, 32]. A previous study demonstrated that strict LDL-C control by rosuvastatin might stabilize atheromatous aortic plaques in acute ischemic stroke patients with large plaques ≥ 4 mm thick on TEE[33]. A recent trial, which evaluated the benefit of aggressive LDL-C control (LDL-C < 70 mg/dL) via basal control with statins, reported a significant reduction of major cardiovascular events in patients with ischemic stroke and atherosclerotic disease including aortic arch plaques ≥ 4 mm in thickness[34]. These data suggest that in addition to oral anticoagulant, statin therapy may be a secondary prevention option for these patients.

This study has some limitations. First, we introduced TEE examination for 71.6% of continuous cases. The patients in the group who did not undergo TEE were significantly older (82.9 ± 9.5 years vs 75.6 ± 9.4 years, $P<0.0001$), had a lower prevalence of hypertension (66.7% vs 84.0%, $P<0.05$), predominantly female (64.3 % vs 30.2 %, $P<0.0001$), had a higher prevalence of chronic AF (64.3 % vs 40.6 %, *P*

<0.01), chronic heart failure (38.1% vs 21.7%, $P<0.05$), and higher NIHSS scores (20.5 vs 6.5, $P<0.0001$) than those in the group evaluated by TEE **(Supplementary Table 1)**. The most common reason for not performing TEE was the severity of patients' clinical status. Second, because this was a retrospective study performed at a single stroke center on a small patient population, further prospective studies in a large population are warranted.

5. Conclusion

In this study, 38.7% patients with acute ischemic stroke showed concomitant CAPs and non-valvular AF. Particular attention should be paid to those who are elderly and have diabetes or low HDL-C, to ascertain whether they have potential sources of emboli other than AF.

Acknowledgements

We would like to thank Editage (www.editage.com) for English language editing.

Funding Support

None.

Conflict of Interest

R.T. reports personal fees from honoraria: not related to the current work: Takeda Pharmaceutical Co., Ltd.; Nippon Boehringer Ingelheim Co., Ltd; Dai-Nippon Sumitomo Pharma Co., Ltd.; Bayer Yakuhin, Ltd; Otsuka Pharmaceutical Co., Ltd; Pfizer Japan Inc.; DAIICHI SANKYO Co., Ltd.; Eisai Co., Ltd.; Bristol-Myers Squibb Co.; Stryker Japan; and Sanofi K.K.

S.F. received lecture fee from Takeda Pharmaceutical Co., Ltd.; Nippon Boehringer Ingelheim Co., Ltd; Dai-Nippon Sumitomo Pharma Co., Ltd.; Bayer Yakuhin, Ltd; Otsuka Pharmaceutical Co., Ltd; Pfizer Japan Inc.; DAIICHI SANKYO Co., Ltd.; Eisai Co., Ltd.; Bristol-Myers Squibb Co.; Sanofi K.K.; and MSD K. K.

References

1) Macleod MR, Amarenco P, Davis SM, Donnan GA: Atheroma of the aortic arch: An important and poorly recognised factor in the aetiology of stroke. Lancet Neurol, 2004; 3: 408-414
2) Toyoda K, Yasaka M, Nagata S, Yamaguchi T: Aortogenic embolic stroke: A transesophageal echocardiographic approach. Stroke, 1992; 23: 1056-1061
3) Capmany RP, Ibañez MO, Pesquer XJ: Complex atheromatosis of the aortic arch in cerebral infarction. Curr Cardiol Rev, 2010; 6: 184-193
4) Ueno Y, Yamashiro K, Tanaka R, Kuroki T, Hira K, Kurita N, Urabe T, Hattori N: Emerging risk factors for recurrent vascular events in patients with embolic stroke of undetermined source. Stroke, 2016; 47: 2714-2721
5) Ntaios G, Pearce LA, Meseguer E, Endres M, Amarenco P, Ozturk S, Lang W, Bornstein NM, Molina CA, Pagola J, Mundl H, Berkowitz SD, Liu YY, Sen S, Connolly SJ, Hart RG: Aortic arch atherosclerosis in patients with embolic stroke of undetermined source: An exploratory analysis of the NAVIGATE ESUS trial. Stroke, 2019; 50: 3184-3190
6) Rahman F, Kwan GF, Benjamin EJ: Global epidemiology of atrial fibrillation. Nat Rev Cardiol, 2014; 11: 639-654
7) Bai Y, Wang YL, Shantsila A, Lip GYH: The global burden of atrial fibrillation and stroke: A systematic review of the clinical epidemiology of atrial fibrillation in Asia. Chest, 2017; 152: 810-820
8) Blackshear JL, Pearce LA, Hart RG, Zabalgoitia M, Labovitz A, Asinger RW, Halperin JL: Aortic plaque in atrial fibrillation: Prevalence, predictors, and thromboembolic implications. Stroke, 1999; 30: 834-840
9) Samuels OB, Joseph GJ, Lynn MJ, Smith MA, Chimowitz MI: A standardized method for measuring intracranial arterial stenosis. AJNR Am J Neuroradiol, 2000; 21: 643-646
10) Di Tullio MR, Russo C, Jin Z, Sacco RL, Mohr JP, Homma S; Patent Foramen Ovale in Cryptogenic Stroke Study Investigators: Aortic arch plaques and risk of recurrent stroke and death. Circulation, 2009; 119: 2376-2382
11) Okura H, Kataoka T, Yoshiyama M, Yoshikawa J, Yoshida K: Aortic atherosclerotic plaque and long-term prognosis in patients with atrial fibrillation - a transesophageal echocardiography study. Circ J, 2013; 77: 68-72
12) Sugioka K, Takagi M, Sakamoto S, Fujita S, Ito A, Iwata S, Matsumura Y, Nakagawa M, Doi A, Miki Y, Yoshiyama M, Ueda M: Predictors of silent brain infarction on magnetic resonance imaging in patients with nonvalvular atrial fibrillation: A transesophageal echocardiographic study. Am Heart J, 2015; 169: 783-790
13) Yang PS, Kim TH, Uhm JS, Kim JY, Joung B, Lee MH, Pak HN: Clinical characteristics of complex aortic plaque in patients with non-valvular atrial fibrillation. Int J Cardiol, 2017; 230: 85-90
14) Amarenco P, Cohen A, Tzourio C, Bertrand B, Hommel M, Besson G, Chauvel C, Touboul PJ, Bousser MG: Atherosclerotic disease of the aortic arch and the risk of ischemic stroke. N Engl J Med, 1994; 331: 1474-1479
15) Kitano T, Nezu T, Shiromoto T, Kubo S, Uemura J, Wada Y, Yagita Y: Association between absolute eosinophil count and complex aortic arch plaque in patients with acute ischemic stroke. Stroke, 2017; 48: 1074-1076
16) Guidoux C, Mazighi M, Lavallée P, Labreuche J, Meseguer E, Cabrejo L, Messika-Zeitoun D, Escoubet B, Touboul PJ, Steg PG, Amarenco P: Aortic arch atheroma in transient ischemic attack patients. Atherosclerosis, 2013; 23: 124-128
17) Moreno PR, Fuster V: New aspects in the pathogenesis of diabetic atherothrombosis. J Am Coll Cardiol, 2004; 44:

2293-2300
18) Yahagi K, Kolodgie FD, Lutter C, Mori H, Romero ME, Finn AV, Virmani R: Pathology of human coronary and carotid artery atherosclerosis and vascular calcification in diabetes mellitus. Arterioscler Thromb Vasc Biol, 2017; 37: 191-204
19) Esposito L, Saam T, Heider P, Bockelbrink A, Pelisek J, Sepp D, Feurer R, Winkler C, Liebig T, Holzer K, Pauly O, Sadikovic S, Hemmer B, Poppert H: MRI plaque imaging reveals high-risk carotid plaques especially in diabetic patients irrespective of the degree of stenosis. BMC Med Imaging, 2010; 10: 27
20) Kojima K, Kimura S, Hayasaka K, Mizusawa M, Misawa T, Yamakami Y, Sagawa Y, Ohtani H, Hishikari K, Sugiyama T, Hikita H, Takahashi A: Aortic plaque distribution, and association between aortic plaque and atherosclerotic risk factors: An aortic angioscopy study. J Atheroscler Thromb, 2019; 26: 997-1006
21) Lorenzatti AJ, Toth PP: New perspectives on atherogenic dyslipidaemia and cardiovascular disease. Eur Cardiol, 2020; 15: 1-9
22) Calabresi L, Gomaraschi M, Simonelli S, Bernini F, Franceschini G: HDL and atherosclerosis: Insights from inherited HDL disorders. Biochim Biophys Acta, 2015; 185: 13-18
23) Toyoda K, Yasaka M, Iwade K, Nagata K, Koretsune Y, Sakamoto T, Uchiyama S, Gotoh J, Nagao T, Yamamoto M, Takahashi JC, Minematsu K, and for the Bleeding with Antithrombotic Therapy (BAT) Study Group: Dual antithrombotic therapy increases severe bleeding events in patients with stroke and cardiovascular disease: A prospective, multicenter, observational study. Stroke, 2008; 39: 1740-1745
24) Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, Ezekowitz M, Oldgren J, Eikelboom JW, Reilly PA, Yusuf S: Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation, 2013; 127: 634-640
25) Shah R, Hellkamp A, Lokhnygina Y, Becker RC, Berkowitz SD, Breithardt G, Hacke W, Halperin JL, Hankey GJ, Fox KA, Nessel CC, Mahaffey KW, Piccini JP, Singer DE, Patel MR, ROCKET AF Steering Committee Investigators: Use of concomitant aspirin in patients with atrial fibrillation: Findings from the ROCKET AF trial. Am Heart J, 2016; 179: 77-86
26) Alexander JH, Lopes RD, Thomas L, Alings M, Atar D, Aylward P, Goto S, Hanna M, Huber K, Husted S, Lewis BS, McMurray JJ, Pais P, Pouleur H, Steg PG, Verheugt FW, Wojdyla DM, Granger CB, Wallentin L: Apixaban vs. warfarin with concomitant aspirin in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J, 2014; 35: 224-232
27) Xu H, Ruff CT, Giugliano RP, Murphy SA, Nordio F, Patel I, Shi M, Mercuri M, Antman EM, Braunwald E: Concomitant use of single antiplatelet therapy with edoxaban or warfarin in patients with atrial fibrillation: analysis from the ENGAGE AF-TIMI48 trial. J Am Heart Assoc, 2016; 5: e002587
28) Masunaga N, Abe M, Ogawa H, Aono Y, Ikeda S, Doi K, An Y, Ishii M, Iguchi M, Esato M, Tsuji H, Wada H, Lip GY, Akao M, on behalf of the Fushimi AF Registry Investigators: Current status, time trends and outcomes of combination therapy with oral anticoagulant and antiplatelet drug in patients with atrial fibrillation-The Fushimi AF Registry. Circ J, 2018; 82: 2983-2991
29) Yasuda S, Kaikita K, Akao M, Ako J, Matoba T, Nakamura M, Miyauchi K, Hagiwara N, Kimura K, Hirayama A, Matsui K, Ogawa H, AFIRE Investigators: Antithrombotic therapy for atrial fibrillation with stable coronary disease. NEJM, 2019; 381: 1103-1113
30) Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillesen H, Simunovic L, Szarek M, Welch KM, Zivin JA, Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators: High-dose atorvastatin after stroke or transient ischemic attack. NEJM, 2006; 355: 549-559
31) Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, Johnston SC, Kasner SE, Kittner SJ, Mitchell PH, Rich MW, Richardson D, Schwamm LH, Wilson JA, American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease: Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: A guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke, 2014; 45: 2160-2236
32) The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee: Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. Cerebrovasc Dis, 2008; 25: 457-507
33) Ueno Y, Yamashiro K, Tanaka Y, Watanabe M, Miyamoto N, Shimada Y, Kuroki T, Tanaka R, Miyauchi K, Daida H, Hattori N, Urabe T: Rosuvastatin may stabilize atherosclerotic aortic plaque: Transesophageal echocardiographic study in the EPISTEME trial. Atherosclerosis, 2015; 239: 476-482
34) Amarenco P, Kim JS, Labreuche J, Charles H, Giroud M, Lee BC, Mahagne MH, Nighoghossian N, Steg PG, Vicaut E, Bruckert E, Treat Stroke to Target Investigators: Benefit of Targeting a LDL (Low-Density Lipoprotein) cholesterol <70 mg/dL during 5 years after Ischemic stroke. Stroke, 2020; 51: 1231-1239

Supplementary Table 1. Comparison of the clinical features between the group with and without TEE evaluation

	TEE (-)	TEE (+)	*P*
N= 148	42	106	
Age	82.9 ± 9.5	75.6 ± 9.4	< 0.0001
Gender (F)	27 (64.3%)	32 (30.2%)	0.0001
BMI	22.3 ± 4.5	22.9 ± 3.4	0.33
Hypertension	28 (66.7%)	89 (84.0%)	< 0.05
Dyslipidemia	17 (40.5%)	48 (45.3%)	0.57
Diabetes mellitus	13 (31.0%)	38 (35.9%)	0.60
Chronic kidney disease	22 (52.4%)	53 (50.0%)	0.79
Hemodialysis	1 (2.4%)	3 (2.8%)	0.88
Chronic AF	27 (64.3%)	43 (40.6%)	< 0.01
Paroxismal AF	15 (35.7%)	63 (59.4%)	< 0.01
Chronic heart failure	16 (38.1%)	23 (21.7%)	< 0.05
Current smoke	5 (13.2%)	18 (17.1%)	0.57
Past medical history			
Ischemic stroke	12 (28.6%)	25 (23.6%)	0.53
Coronary artery disease	6 (14.3%)	12 (11.3%)	0.62
Peripheral artery disease	1 (2.4%)	5 (4.7%)	0.52
$CHADS_2$ score	3 (0 - 6)	2 (0 - 6)	0.12
CHA_2DS_2-VASc score	5 (1 - 8)	4 (0 - 8)	< 0.01
Pre-stroke medication			
Antiplatelet	10 (23.8%)	20 (18.9%)	0.50
Oral anticoagulant	10 (23.8%)	41 (38.7%)	0.08
Warfarin	3 (7.1%)	18 (17.0%)	0.09
Direct oral anticoagulation	6 (14.3%)	17 (16.0%)	0.79
Statin	3 (42.9%)	23 (21.7%)	0.20
Data			
LDL-C (mg/dl)	111.6 ± 33.8	111.0 ± 34.1	0.94
HDL-C (mg/dl)	59.3 ± 16.4	56.3 ± 16.3	0.39
TG (mg/dl)	90.5 ± 33.6	115.9 ± 84.9	0.29
BS (mg/dl)	163.4 ± 69.5	136.6 ± 40.7	< 0.05
HbA1c (%)	6.5 ± 1.5	6.3 ± 1.1	0.65
BNP (pg/dl)	269.1 ± 242.6	221.0 ± 286.8	0.08
NIHSS	20.5 (0 - 39)	6.5 (0 - 39)	< 0.0001

LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; BS, blood sugar; HbA1c, glycohemoglobin A1c; BNP, brain natriuretic peptide; NIHSS, National Institutes of Health Stroke Scale score; NS, non-significant; TEE, transesophageal echocardiography