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 CHADS2 and CHA2DS2-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 \( \geq 84 \) 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.
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 database 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 CHADS2 or CHA2DS2-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.

2.3. Carotid Echosonography

Carotid echosonography was performed using a commercially available ultrasound imaging system (ProSound a7, 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. 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 χ2 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 Non-valvular Atrial Fibrillation

We identified 106 consecutive patients with non-valvular 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<
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\(_2\)DS\(_2\)-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\(_2\)DS\(_2\)-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 1. Comparison of clinical and demographic features of patients according to the presence of CAPs |
|---------------------------------------------|-----------------|-----------------|
| N=106                                      | CAPs (-)        | CAPs (+)        |
| Age                                        | 65              | 41 (38.7%)      |
| SEX (F)                                    | 72.7 ± 9.0      | 80.2 ± 8.2      |
| Body mass index                            | 19 (29.2%)      | 13 (31.7%)      |
| Hypertension                               | 23.1 ± 3.8      | 22.6 ± 2.7      |
| Dyslipidemia                               | 51 (78.5%)      | 38 (92.7%)      |
| Diabetes mellitus                          | 27 (41.5%)      | 21 (51.2%)      |
| Chronic kidney disease                     | 17 (26.2%)      | 21 (51.2%)      |
| Hemodialysis                               | 26 (40%)        | 27 (65.9%)      |
| Medical history                            | 7.7%            | 0.1             |
| Ischemic stroke                            | 12 (18.5%)      | 13 (31.7%)      |
| Coronary artery disease                    | 5 (7.7%)        | 7 (17.1%)       |
| Peripheral artery disease                  | 1 (1.5%)        | 4 (9.8%)        |
| CHADS\(_2\) score                         | 2 (0-6)         | 3 (0-5)         |
| CHA\(_2\)DS\(_2\)-VASc score              | 3 (0-8)         | 4 (1-7)         |
| Presroke med                                |                |                |
| Antiplatelet therapy                       | 9 (13.9%)       | 11 (26.8%)      |
| Oral anticoagulation                       | 28 (43.1%)      | 13 (31.2%)      |
| Warfarin                                   | 14 (21.5%)      | 4 (9.8%)        |
| Direct oral anticoagulation                | 12 (18.5%)      | 5 (12.2%)       |
| Statin                                     | 11 (16.9%)      | 12 (29.3%)      |
| Data                                       |                |                |
| LDL-C (mg/dL)                              | 108.8 ± 33.1    | 114.5 ± 35.8    |
| HDL-C (mg/dL)                              | 60.3 ± 15.7     | 50 ± 15.3       |
| TG (mg/dL)                                 | 113.4 ± 93.8    | 119.8 ± 69.9    |
| BS (mg/dL)                                 | 134.2 ± 41.7    | 140.4 ± 39.4    |
| HbA1c (%)                                  | 6.1 ± 0.97      | 6.5 ± 1.2       |
| BNP (pg/dl)                                | 214.3 ± 316.5   | 231.6 ± 235.6   |
| Clinical and imaging data                  |                |                |
| NIHSS                                      | 10.4 ± 9.9      | 10.9 ± 9.3      |
| Intracranial artery stenosis               | 5 (7.7%)        | 11 (26.8%)      |
| Carotid artery stenosis                    | 5 (7.7%)        | 9 (22%)         |
| Multiple infarcts on DWI                   | 32 (51.6%)      | 22 (53.7%)      |
| Cortical infarcts on DWI                   | 46 (74.2%)      | 31 (75.6%)      |
| Multi-vascular territory infarcts on DWI   | 6 (9.7%)        | 4 (10%)         |

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
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, CHADS2, and CHA2DS2-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 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 2. Association between vascular risk factors and presence of CAPs in NVAF

| Risk Factor | Univariate OR (95% CI) | P value | Multivariate 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 | 1.5 (0.60–3.92) | 0.37 |
| CHADS2 score | 1.7 (1.20–2.33) | <0.01 | 1.5 (0.71–3.33) | 0.37 |
| CHA2DS2-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).
Table 3. Age-dependent risk of CAPs in patients with acute ischemic stroke with non-valvular AF

| Age       | Univariate | Multivariate |
|-----------|------------|--------------|
|           | 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. 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%) in patients with diabetes mellitus and peripheral arterial disease were 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.

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 vas vasorum neovascularization; 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.

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. 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. Another study showed that the presence of diabetes was an independent risk factor for vulnerable aortic plaque burden, as evaluated by aortic angiography. 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{11}, based on a study of 108 consecutive patients with AF who underwent TEE, including 21 patients (19\%) with AoP $\geq 4$ mm and 24 patients (22.2\%) with previous stroke. The frequency of cardiovascular events, including ischemic stroke, was significantly higher in patients with AoP $\geq 4$ mm than in those with AoP $<4$ mm, and AoP $\geq 4$ 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 transcatheater AF ablation\textsuperscript{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\textsubscript{2} score $\geq 2$, 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\textsuperscript{23}. Sub-analyses 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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{30}. The American and European guidelines both recommend intensive lipid lowering therapy using statins after TIA or ischemic stroke with atherosclerotic origin\textsuperscript{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 $\geq 4$ mm thick on TEE\textsuperscript{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 $\geq 4$ mm in thickness\textsuperscript{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 ($82.9 \pm 9.5$ years vs $75.6 \pm 9.4$ 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.

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

|                      | TEE (-) | TEE (+) | \( P \)  |
|----------------------|---------|---------|----------|
| **N**                | 148     | 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   |
| Paroxysmal 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    |
| CHADS2 score         | 3 (0 - 6) | 2 (0 - 6)  | 0.12    |
| CHA2DS2-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