disease. For these patients, a lower target blood pressure than for patients without chronic kidney disease is generally needed, and initial antihypertensive treatments should include an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to improve kidney outcomes.[113] Strategies for management of chronic kidney disease often depend on the health-care system in individual countries.[2] Living in a country with low socioeconomic status increases the risk of progressive chronic kidney disease.[114] Because renal replacement treatments are costly, care for patients with end-stage kidney disease is often insufficient in developing countries and might further increase stroke risk of patients with kidney disease in such countries.

What is the burden of stroke in patients with end-stage kidney disease?

Stroke is common in patients with end-stage kidney disease, both in those undergoing haemodialysis[115] and those undergoing peritoneal dialysis.[116] The risk of stroke in patients on dialysis is four to ten times higher than that in the general population.[117] One study found that stroke in patients with nephropathy caused by either nephrosclerosis or diabetes mellitus was likely to develop early after starting dialysis, whereas in most patients with chronic glomerulonephritis who had stroke events these occurred more than 36 months after starting dialysis treatment.[118] Supportive findings from a Japanese cohort study of 2977 patients with chronic kidney disease with eGFR of 10–59 mL/min per 1·73 m² showed that patients with chronic glomerulonephritis had a lower brachial-ankle pulse wave velocity—a marker of atherosclerotic disease—than those with diabetic nephropathy or non-chronic glomerulonephritic kidney disease.[119] This finding supports the hypothesis that kidney impairment in combination with other cardiovascular risk factors accelerates atherosclerosis and raises the risk of the development of stroke in the predialysis stages. By contrast, characteristics unique to dialysis, such as drastic haemodynamic change and consequent high variability of blood pressure, dialysate and anticoagulants, vascular access, dialysis amyloidosis, vascular calcification, and years on dialysis, can be triggers of both ischaemic and haemorrhagic strokes.[120,121]

Search strategy and selection criteria

We searched PubMed for articles published in English up to Oct 31, 2013, with the search terms "kidney", "renal", "haemodialysis", "brain", "stroke", "cerebral infarction", "intracerebral haemorrhage", "cerebrovascular", "white matter", "microbleed", "carotid artery", "cognition", and "dementia". Additionally, we searched references from relevant articles and those from a personal library. The final reference list was generated on the basis of originality and relevance to topics covered in this Review.

Acute management of stroke is further restricted in patients with end-stage kidney disease compared with patients with milder chronic kidney disease; for example, by the contraindication of some pharmacotherapies including the newer oral anticoagulants and the difficulty of continuing dialysis in the same physical condition as before when severe neurological deficits remain. Since patients on haemodialysis often develop stroke while at dialysis clinics,[115] good emergent cooperation between dialysis clinics and stroke centres is needed to increase the chance that patients receive hyperacute thrombolysis and thrombectomy. Intravenous thrombolysis is not contraindicated for patients with end-stage kidney disease;[122] however, even thrombolysis experts often have limited experience with this treatment in these patients.[123]

Conclusions and future directions

Our review of the strong associations of chronic kidney disease with stroke and subclinical cerebrovascular diseases shows that the time has come for neurology to meet nephrology. Preventive management strategies for chronic kidney disease and for cerebrovascular diseases have a lot in common. Additionally, chronic kidney disease further increases the risk of cerebrovascular diseases in patients with vascular risk factors. Large clinical trials have generally excluded patients with advanced renal dysfunction because of safety issues, and, therefore, establishment of novel treatments for such patients is often difficult. A practical strategy to expand stroke management in patients with chronic kidney disease might be to expand the indications of existing pharmacotherapies that are limited at present because of their major excretion from the kidney, by developing dosages and intervals of drug administration. Development of drugs with both neuroprotective and nephroprotective effects is also awaited. A thorough understanding of the cerebrorenal interaction is important to minimise the burden of cerebrovascular disease in patients with chronic kidney disease. Attempts to achieve these goals will benefit from collaboration between neurologists and nephrologists.

Contributors

The authors contributed equally to the planning and writing of this Review, KT mainly from a clinical perspective and TN mainly from an epidemiological perspective.

Declaration of interests

We declare no competing interests.

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Stroke Education Program of Act FAST for Junior High School Students and Their Parents

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Background: We produced a stroke education program using the FAST (facial droop, arm weakness, speech disturbance, time to call an ambulance) mnemonic. *Aims:* The aim of this study is to examine efficacy of our education program for junior high school students and their parents. *Methods:* One hundred ninety students of 3 junior high schools (aged 12-13 years) and their parents were enrolled. Students received a 45-minute lesson of stroke enlightenment using the FAST mnemonic. Enlightenment items, such as a magnet poster, were distributed. Parents were educated indirectly from their child. Surveys of stroke knowledge were examined at baseline, immediately after the lesson, and at 3 months after the lesson. *Results:* For the students, correct answers at 3 months were significantly higher than those at baseline in questions of facial palsy (98% versus 33%), speech disturbance (98% versus 54%), numbness on one side (64% versus 42%), weakness on one side (80% versus 51%), calling an ambulance (88% versus 60%), alcohol drinking (85% versus 65%), smoking (70% versus 43%), dyslipidemia (58% versus 46%), hyperglycemia (59% versus 48%), and obesity (47% versus 23%). At 3 months, the parents answered more correctly questions of facial palsy (93% versus 66%), calling an ambulance (95% versus 88%), and alcohol drinking (65% versus 51%) than at baseline. At 3 months, 96% of students and 78% of parents answered the FAST mnemonic correctly. *Conclusions:* Our stroke education program improved stroke knowledge, especially the FAST message, for junior high school students and their parents. **Key Words:** School-based intervention—stroke enlightenment—stroke knowledge—emergent medical service—prehospital delay.

Introduction

Stroke is a major cause of disability and a major cause of death worldwide. Shortening the time from the onset of stroke symptoms to hospital arrival is important for effective stroke treatment because the early administration of recombinant tissue-type plasminogen activator is beneficial for stroke outcome.[1,2] Both a reduction in the risk of stroke and a decrease in prehospital delay after the onset of stroke are considered to depend on the level of stroke knowledge in the general population.[3] Education program and the target population for education are essential for effective stroke enlightenment. Retained knowledge of stroke awareness results in appropriate

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action of calling emergent medical services (EMS) on stroke onset. Although there are several reports of public education for stroke enlightenment,[4-9] there are only a few studies in children.[10-12] School-based interventions of stroke enlightenment are beneficial for students and a promising means for delivering stroke message to their parents or grandparents.[10-12] The methods used to educate children for stroke enlightenment would be different depending on age, ethnicity, and socioeconomic status of their parents.

Aims

The aim of this study was to examine the efficacy of our stroke education program for junior high school students and their parents.

Methods

Stroke Enlightenment Items

For enlightenment of stroke sign and symptoms, we used "FAST" derived from the Cincinnati Prehospital Stroke Scale, where F is face numbness or weakness, A is arm numbness or weakness, and S is slurred speech or difficulty speaking or understanding.[5,13] We produced a poster measuring 600 × 400 mm, a magnet poster measuring 150 × 105 mm, and a paper file measuring 310 × 220 mm that were printed with the FAST message (Fig 1). School items such as a pen and sticky note with the FAST mnemonic were also produced.

Subjects and Study Design

This study was exempted from approval by the institutional review board based on our domestic guideline because of the use of only an anonymized and untraceable data set. We enrolled 190 students in 6 classes of the first grade of 3 private junior high schools (aged 12-13 years) and their parents. We conducted stroke lessons between October 2010 and March 2011. Students received a 45-minute lesson performed by stroke neurologists. The lesson was composed of a lecture with slide show and a short role-play with students. In the lecture, students were taught stroke risk factors, stroke signs and symptoms, and appropriate urgent responses when they suspected stroke by using FAST mnemonic. Students could understand the FAST mnemonic in English because they had learned the word FAST in English class. In the short role-play, the neurologist acted as an old man just suffering from stroke and students performed in accordance with the FAST mnemonic. At the close of the lesson, we distributed the pen, paper file, magnet posters, sticky notes printed with the FAST message, and papers printed with the lecture slide show to each student. We did not conduct any stroke lessons for the students' parents. Instead, we asked the students to talk about stroke with their parents while showing them the images of the slide show and to place the magnet poster on the kitchen refrigerator. A FAST mnemonic poster was displayed in each classroom for 3 months after the stroke lesson.

For the assessments, multiple-choice and closed-type questionnaires on stroke knowledge (including a total of 7 items for risk factors, 6 items for stroke signs and symptoms, and 1 item for appropriate urgent responses) were filled out by the students at baseline, immediately after the lesson, and at 3 months after the lesson. All data were collected without personal identifiers. For questionnaires at the baseline, questionnaires were distributed to the students within 7 days before the day of the stroke lesson. Students also took the same questionnaires to their parents on the day of the stroke lesson and at 3 months after the lesson. Parents filled out questionnaires before, immediately, and 3 months after talking about stroke with their children. Questionnaires filled out by parents were gathered through their child who took them to their children at school.

Statistical analyses were performed using JMP7.0 (SAS Institute, Inc., Cary, NC). Data are presented as frequencies (%). Data were compared among 3 groups with Fisher exact test: baseline, immediately after the lesson, and 3 months after the lesson. The proportion of selecting "calling EMS" on the identification of stroke signs or symptoms was also assessed with Fisher exact test. A value of P less than .05 was considered to indicate a significant difference.

Result

Assessment for Students

Because a few students were absent from school, the numbers of questionnaires collected immediately and at 3 months after the lesson were 189 (99%) and 187 (98%), respectively. Immediately after the lesson, the frequencies of correct answers for all questions were significantly higher than those at baseline (Table 1). At 3 months after the lesson, the number of students with correct answers of facial palsy (98% versus 33%), speech disturbance (98% versus 54%), numbness on 1 side of body (64% versus 42%), and weakness on 1 side of body (80% versus 51%) were significantly improved. However, severe headache (26% versus 55%) and vision loss (5% versus 17%) were significantly decreased compared with those at baseline. More students answered correctly about calling EMS for stroke (88% versus 60%) and risk factors except hypertension or arrhythmia at 3 months after the lesson compared with those at baseline. The 96% of students who understood the meaning of FAST mnemonic at 3 months after the lesson was similar to that immediately after the lesson.

Assessment for Student's Parents

A total of 183 (96%) questionnaires were filled out by students' parents at baseline, with 155 (82%) immediately,

Figure 1. *FAST message poster for stroke warning signs. FAST represents "F," facial droop; "A," arm weakness; "S, speech disturbance; and "T," time to call an ambulance. The FAST message means that if you recognize one of these symptoms, check the onset time and call an ambulance. These messages are written in Japanese.*

and 175 (92%) at 3 months after the lesson. Parents immediately after the lesson, who chose facial palsy (94% versus 66%), vision loss (46% versus 31%), and speech disturbance (97% versus 91%) as stroke symptoms, 7 correct answers except hypertension as risk factors, and a correct urgent response (97% versus 88%), were significantly higher than those at the baseline (Table 2). At 3 months after the lesson, the number of parents with correct answers of stroke risk factors except alcohol drinking decreased to the same level as those at baseline. However, the correct answer rate of facial palsy (93% versus 66%) and calling EMS (95% versus 88%) persisted as similar to that immediately after the lesson. The 89% of parents who understood correctly the FAST mnemonic immediately after the lesson was similar to that at 3 months after the lesson.

Discussion

Our results showed that our stroke education program by using our homemade items for junior high school students improved their stroke knowledge, especially for the FAST message. Understanding of the FAST message was

Table 1. *The percentages of correct answers to questions about stroke over all 3 surveys for students*

Questions	Baseline (n = 190), %	Immediate after the lesson (n = 189), %	P*	3 months after the lesson (n = 187), %	P*
1. Stroke signs and symptoms					
Headache	55	66	.0359	26	<.0001
Facial palsy	33	98	<.0001	98	<.0001
Vision loss	17	41	<.0001	5	.0003
Speech disturbance	54	97	<.0001	98	<.0001
Numbness on 1 side of the body	42	82	<.0001	64	<.0001
Weakness on 1 side of the body	51	95	<.0001	80	<.0001
2. Adequate action when stroke onset					
Call an ambulance	60	96	<.0001	88	<.0001
3. Stroke risk factors					
Alcohol drinking	65	91	<.0001	85	<.0001
Smoking	43	89	<.0001	70	<.0001
Hypertension	73	97	<.0001	81	.0509
Dyslipidemia	46	85	<.0001	58	.0233
Hyperglycemia	48	81	<.0001	59	.0498
Obesity	23	72	<.0001	47	<.0001
Arrhythmia	39	69	<.0001	43	ns
4. FAST mnemonic					
F = face		100	NA	98	NA
A = arm		99	NA	99	NA
S = speech		100	NA	98	NA
T = time		99	NA	99	NA
All corrected		98	NA	96	NA

Abbreviations: NA, not applicable; ns, nonsignificant.
*Fisher exact test, compared with baseline.

also observed in the students' parents who instructed in stroke enlightenment by their children.

Williams and Noble[10] reported that incorporating cultural elements such as hip-hop music improved retention of stroke knowledge among elementary school children. They also demonstrated the possibility of child-mediated stroke communication from the results of questionnaires for the parents at 1 week after the intervention for the children.[12] Morgenstern et al[11] showed that their stroke enlightenment project, intended for middle school children and their parents/guardians, was beneficial for the children but not for their parents/guardians. In our study, a high rate of correct answers, especially for FAST message, was observed not only immediately but also 3 months after the stroke lesson in students and their parents. The stroke lesson, including the short role-play, would impress the FAST message on students. In addition, our homemade enlightenment items, such as the poster in the classroom, the magnet poster on the refrigerator at home, and stationary (paper file, pen, sticky note with the FAST mnemonic) might fix the FAST message in their minds. On the other hand, stroke symptoms other than FAST, such as severe headache or vision loss, were not recalled by the students after the stroke lesson. Therefore, our items of stroke enlightenment need to be improved for stroke symptoms not involved in the FAST mnemonic and stroke risk factors.

Although our education program was effective in keeping the FAST message in the mind of both students and their parents, it may be difficult to act promptly in calling EMS on the warning signs of stroke in future. Addo et al[14] reported that significant delays in seeking care after stroke still occur after a campaign to promote public awareness of stroke. Fussman et al[15] indicated a lack of association between stroke symptom knowledge and the intent to call EMS in the population-based survey. It would be necessary to repeat education program for fixing stroke knowledge during the junior high school period and to promote motivation for calling EMS by recognition that negative outcomes can be diminished by early awareness as previously indicated.[16] Moreover, not only stroke knowledge but also the presence of bystanders at stroke onset is essential for early arrival at hospital.[17,18] Our school-based stroke education program anticipates that the students would, at some time, play the role of bystander.

There are several limitations to our study. First, our study is not a randomized controlled study. It is difficult to maintain regular lectures of stroke enlightenment of intervention without leakage of the FAST mnemonic to non-intervention classes in the same school during the 3 months of the study period. Although the sample size was not large in this single-arm study, improvement of stroke knowledge was confirmed after our stroke

Table 2. *The percentages of correct answers to questions about stroke over all 3 surveys for parents*

Questions	Baseline (n = 183), %	Immediate after the lesson (n = 155), %	P*	3 months after the lesson (n = 175), %	P*
1. Stroke signs and symptoms					
Headache	83	72	.0128	67	.0006
Facial palsy	66	94	<.0001	93	<.0001
Vision loss	31	46	.0069	25	ns
Speech disturbance	91	97	.0122	95	ns
Numbness on 1 side of the body	75	77	ns	78	ns
Weakness on 1 side of the body	81	86	ns	87	ns
2. Adequate action when stroke onset					
Call an ambulance	88	97	.004	95	.0239
3. Stroke risk factors					
Alcohol drinking	51	75	<.0001	65	.0102
Smoking	73	86	.0049	79	ns
Hypertension	92	96	ns	93	ns
Dyslipidemia	80	91	.0057	77	ns
Hyperglycemia	49	67	.0009	49	ns
Obesity	56	68	.0249	54	ns
Arrhythmia	30	52	<.0001	31	ns
4. FAST mnemonic					
F = face		99	NA	90	NA
A = arm		94	NA	86	NA
S = speech		97	NA	93	NA
T = time		96	NA	86	NA
All corrected		89	NA	78	NA

Abbreviations: NA, not applicable; ns, nonsignificant.
*Fisher exact test, compared with baseline.

education program by the high proportion of follow-up examinations performed by either students or their parents. Second, the junior high school for interventions in the present study were conducted at private schools, and the parents of these students would have higher levels of education and upper socioeconomic status that might associate with the higher level of stroke knowledge at baseline as indicated previously.[6] Further examinations using randomized controlled studies that include several public schools with and without educational intervention will be needed. Third, this is a cross-sectional study, and behavioral change of calling EMS at awareness of stroke was not examined. Time monitoring of prehospital delay in the stroke centers within the area of the intervention of stroke education would be expected. Fourth, the assessments of stroke knowledge were examined by multiple-choice and closed-type questionnaires, possibly associated with an overestimate of stroke knowledge compared with open-ended questions. Finally, this study program requires lessons that are given by medical doctors. It would be necessary to require less assistance to spread the stroke enlightenment widely.

In summary, school-based interventions with our homemade items of stroke enlightenment are beneficial for junior high school students and a promising means for delivering the stroke message to their parents. Stroke enlightenment for the youth would promote a healthy life from a younger age, resulting in the primary prevention of cardiovascular disease in the future.

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ORIGINAL ARTICLE

$CHADS_2$ and CHA_2DS_2-VASc scores as bleeding risk indices for patients with atrial fibrillation: the Bleeding with Antithrombotic Therapy Study

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The $CHADS_2$ and CHA_2DS_2-VASc scores, that is, ischemic stroke risk indices for patients having atrial fibrillation (AF), may also be useful as bleeding risk indices. Japanese patients with AF, who routinely took oral antithrombotic agents were enrolled from a prospective, multicenter study. The $CHADS_2$ and CHA_2DS_2-VASc scores were assessed based on information at entry. Scores of 0, 1 and $\geqslant 2$ were defined as the low, intermediate and high ischemic risk categories, respectively, for each index. Of 1221 patients, 873 took warfarin, 114 took antiplatelet agents and 234 took both. The annual incidence of ischemic stroke was 0.76% in the low-risk category, 1.46% in the intermediate-risk category and 2.90% in the high-risk category by $CHADS_2$ scores, and 1.44, 0.42 and 2.50%, respectively, by CHA_2DS_2-VASc scores. The annual incidence of major bleeding in each category was 1.52, 2.19 and 2.25% by $CHADS_2$, and 1.44, 1.69 and 2.24% by CHA_2DS_2-VASc. After multivariate adjustment, the $CHADS_2$ was associated with ischemia (odds ratio 1.76, 95% confidence interval 1.03–3.38 per 1 −category increase) and the CHA_2DS_2-VASc tended to be associated with ischemia (2.18, 0.89–8.43). On the other hand, associations of the indices with bleeding were weak. In conclusion, bleeding risk increased gradually as the $CHADS_2$ and CHA_2DS_2-VASc scores increased in Japanese antithrombotic users, although the statistical impact was rather weak compared with their predictive power for ischemic stroke.
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Keywords: anticoagulation; atrial fibrillation; intracerebral hemorrhage; stroke; warfarin

INTRODUCTION

Decision-making for thromboprophylaxis needs to balance the risk of ischemic stroke against the risk of major bleeding.[1] Known bleeding risk scores such as $HEMORR_2HAGES$ and HAS-BLED include hypertension, advanced age and history of stroke as their components,[2,3] which are also known risk factors for ischemic stroke and compose the stroke risk scores for patients having atrial fibrillation (AF), such as the $CHADS_2$ and CHA_2DS_2-VASc scores.[4,5] Thus, the $CHADS_2$ and CHA_2DS_2-VASc scores may also be useful as bleeding risk indices.

To determine the incidence and severity of bleeding complications in patients with cardiovascular diseases and stroke treated with oral antithrombotic therapy in Japan, a prospective, multicenter, observational study (the Bleeding with Antithrombotic Therapy (BAT) Study) was conducted. In its initial report of the overall results, adding antiplatelet agents to warfarin or single antiplatelet therapy doubled the risk of life-threatening or major bleeding events.[6] In the second report, an increase in blood pressure levels during antithrombotic medication was positively associated with the development of intracerebral hemorrhage.[7] The series of the findings from the BAT register indicate that patients who require pharmacotherapeutic prevention from ischemic events are also high-risk subjects for bleeding events. Thus, it is important to ascertain the power of known ischemia-risk indices for prediction of bleeding events.

The associations between the $CHADS_2$/CHA_2DS_2-VASc scores of AF patients and the development of bleeding events, as well as ischemic stroke, were examined in the present study.

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METHODS

A total of 4009 patients (2728 men, 69 ± 10 years old) who were taking oral antiplatelet agents or warfarin for cardiovascular or cerebrovascular diseases were enrolled in the BAT Study from 19 stroke and cardiovascular centers in Japan (see Appendix) and were observed for 2–30 months between October 2003 and March 2006. The study protocol, inclusion/exclusion criteria and general results were published previously.[6,7] The medical ethics review boards of the participating institutes approved the study protocol, and all patients provided their written informed consent.

In the present sub-study, AF patients were enrolled from the BAT register. AF was defined by a diagnosis at entry based on a confirmed history or identification on ECG. Baseline data included components of the $CHADS_2$ and CHA_2DS_2-VASc scores, as well as of neoplasm, liver cirrhosis, hypercholesterolemia, current smoking, alcohol consumption, systolic and diastolic blood pressure levels and antithrombotic medication at entry. Definitions of these comorbidities and cardiovascular risk factors were the same as those in the previous study.[6] Scores of 0, 1 and $\geqslant 2$ were defined as the low, intermediate and high ischemic risk categories, respectively, for each index.[5,8]

The outcomes included ischemic stroke and bleeding events during the observation period. Bleeding events were defined as life-threatening or major bleeding events according to the definition by the Management of ATherothrombosis with Clopidogrel in High-risk patients with recent transient ischemic attack or ischemic stroke study.[9] Briefly, life-threatening bleeding was defined as any fatal bleeding event, a drop in hemoglobin of $\geqslant 50\,g\,l^{-1}$, hemorrhagic shock, symptomatic intracranial hemorrhage or transfusion of $\geqslant 4$ units of red blood cells. Major bleeding was defined as significantly disabling, severe intraocular bleeding or transfusion of $\leqslant 3$ units of red blood cells. Secondary hemorrhagic transformation of an ischemic stroke was not regarded as a bleeding event.

Statistics

All analyses were performed using the JMP 8 statistical software (SAS Institute, Cary, NC, USA). To compare baseline clinical characteristics among the three ischemic risk categories according to the $CHADS_2$ and CHA_2DS_2-VASc scores, one-way factorial analysis of variance with *post-hoc* comparison by Dunnett's test (with the high-risk category as control) was used for continuous variables and the χ^2-test was used for categorical variables. Multivariate logistic regression analysis was performed using a forced entry method of baseline clinical characteristics to examine the associations of the $CHADS_2$ and CHA_2DS_2-VASc scores with risks of ischemic stroke and bleeding events, as well as to examine those of the components of the CHA_2DS_2-VASc score. A P-value <0.05 was considered significant.

Table 1 Baseline clinical characteristics

		$CHADS_2$			*CHA_2DS_2-VASc*		
	Total	*Low*	*Intermediate*	*High*	*Low*	*Intermediate*	*High*
Number	1221	186 (15.2%)	283 (23.2%)	752 (61.6%)	53 (4.3%)	163 (13.4%)	1005 (82.3%)
Observation period, months	19.4 (13.8–23.3)	17.4 (13.3–23.0)	18.6 (13.1–23.2)	20.9 (14.2–23.6)†	17.2 (10.6–22.8)	17.9 (13.6–23.0)	20.2 (13.8–23.4)*
Age, years	70 ± 10	63 ± 9	69 ± 10	72 ± 8†	55 ± 8	62 ± 9	72 ± 8†
Female	376 (30.8%)	67 (36.1%)	76 (26.9%)	233 (31.0%)	0	39 (23.9%)†	337 (33.5%)†
Components of the $CHADS_2$ score							
Congestive heart failure	101 (8.3%)	0	20 (7.1%)	81 (10.8%)†	0	7 (4.3%)	94 (9.4%)†
Hypertension	634 (51.9%)	0	146 (51.6%)	488 (64.9%)†	0	46 (28.2%)	588 (58.5%)†
65–4 Years old	443 (36.3%)	94 (50.5%)	102 (36.0%)	247 (32.9%)†	0	63(38.7%)	380 (37.8%)†
75 Years old or older	438 (35.9%)	0	87 (30.7%)	351 (46.9%)†	0	0	438 (43.6%)†
Diabetes mellitus	264 (21.6%)	0	30 (10.6%)	234 (31.1%)†	0	8 (4.9%)	256 (25.5%)†
Prior cerebral ischemia	541 (44.3%)	0	0	541 (71.9%)†	0	0	541 (53.8%)†
Prior thromboembolism	11 (0.9%)	0	1 (0.4%)	10 (1.3%)	0	0	11 (1.1%)
Vascular disease	64 (5.2%)	5 (2.7%)	21 (7.4%)	38 (5.1%)	0	0	64 (6.4%)
Comorbidities							
Neoplasm	96 (7.9%)	13 (7.0%)	22 (7.8%)	61 (8.1%)	2 (3.8%)	10 (6.1%)	84 (8.4%)
Liver cirrhosis	40 (3.3%)	9 (4.8%)	6 (2.1%)	25 (3.3%)	2 (3.8%)	5 (3.1%)	33 (3.3%)
Risk factors							
Hypercholesterolemia	375 (30.7%)	41 (22.0%)	83 (29.3%)	251 (33.4%)†	12 (22.6%)	36 (22.1%)	327 (32.5%)*
Current smoking	156 (12.8%)	27 (14.5%)	38 (13.4%)	91 (12.1%)	11 (20.8%)	30 (18.4%)	115 (11.4) †
Alcohol consumption	53 (4.3%)	5 (2.7%)	13 (4.6%)	35 (4.7%)	3 (5.7%)	6 (3.7%)	44 (4.4%)
Systolic blood pressure, mmHg	129 ± 18	123 ± 16	130 ± 18	131 ± 19†	120 ± 15	126 ± 18	130 ± 18†
Diastolic blood pressure, mm Hg	75 ± 11	72 ± 12	76 ± 12	75 ± 11†	72 ± 16	74 ± 11	75 ± 11
Antithrombotic medication				†			*
Warfarin alone	873 (71.5%)	141 (75.8%)	191 (67.5%)	541 (71.9%)	38 (71.7%)	120 (73.6%)	715 (71.1%)
Antiplatelets alone	114 (9.3%)	24 (12.9%)	35 (12.4%)	55 (7.3%)	8 (15.1%)	22 (13.5%)	84 (8.4%)
Both	234 (19.2%)	21 (11.3%)	57 (20.1%)	156 (20.7%)	7 (13.2%)	21 (12.9%)	206 (20.5%)

Data are medians (interquartile range) for the observation period, means ± s.d. for age and blood pressure, and percent of patients for others.
*$P<0.05$, †$P<0.01$ among three groups.
$CHADS_2$ scores in high-risk category group; 2: 289 patients, 3: 248 patients, 4: 164 patients, 5: 48 patients, 6: 3 patients.
CHA_2DS_2-VASc scores in high-risk category group; 2: 240 patients, 3: 260 patients, 4: 231 patients, 5: 165 patients, 6: 89 patients, 7: 18 patients, 8: 2 patients.

RESULTS

A total of 1221 patients (376 women, 70 ± 10 years old (mean ± s.d.)) were studied. Their baseline characteristics are listed in Table 1. In total, 101 patients (8.3%) had congestive heart failure, 634 (51.9%) had hypertension, 443 (36.3%) were between 65 and 74 years old, 438 (35.9%) were 75 years old or older, 264 (21.6%) had diabetes, 545 (44.6%) had either prior ischemic stroke/transient ischemic attack or prior thromboembolism and 64 (5.2%) had vascular diseases. Overall, 186 patients belonged to the low-risk category, 283 to the intermediate-risk category and 752 to the high-risk category by $CHADS_2$ scores, and 53, 163 and 1005 patients, respectively, by the CHA_2DS_2-VAS scores. As antithrombotic medications, 873 patients (71.5%) took warfarin, 114 (9.3%) took antiplatelet agents (including 14 patients taking dual antiplatelet agents) and 234 (19.2%) took both (including 19 patients taking warfarin plus dual antiplatelet agents). The median international normalized ratio at entry was 1.95 (interquartile range 1.67–2.30) for warfarin users.

During the median observation period of 19.4 months, 40 ischemic stroke and 39 bleeding events occurred. The annual incidence of both events gradually increased as the $CHADS_2$ risk category became higher, and that of bleeding increased gradually as the CHA_2DS_2-VASc risk category became higher (Figure 1). After adjustment for antithrombotic medication (model 1), the $CHADS_2$ score was associated (odds ratio 1.76, 95% confidence interval 1.04–3.38 per 1 −category increase; 1.35, 1.05–1.74 per 1 −point increase) and the CHA_2DS_2-VASc score tended to be associated (2.20, 0.91–8.46 per 1 −category increase; 1.23, 1.01–1.51 per 1 −point increase) with ischemia (Table 2). After further adjustment for neoplasm, liver cirrhosis, hypercholesterolemia, current smoking and alcohol consumption (model 2), the $CHADS_2$ score was associated (odds ratio 1.76, 95% confidence interval 1.03–3.38 per 1 −category increase; 1.33, 1.03–1.73 per 1 −point increase) and the CHA_2DS_2-VASc tended to be associated (2.18, 0.89–8.43 per 1 −category increase; 1.21, 0.99–1.49 per 1 −point increase) with ischemia. On the other hand, there were no significant associations of the indices with bleeding after multivariate adjustment.

Finally, associations of components of the CHA_2DS_2-VASc score with risks of ischemic stroke and bleeding events were also determined (Table 3). Among the components, 'stroke and thromboembolism' tended to be associated with ischemic stroke (odds ratio 1.81, 95% confidence interval 0.93–3.66, $P = 0.073$) and '75 years or older' tended to be associated with bleeding events (2.31, 0.96–6.45, $P = 0.064$).

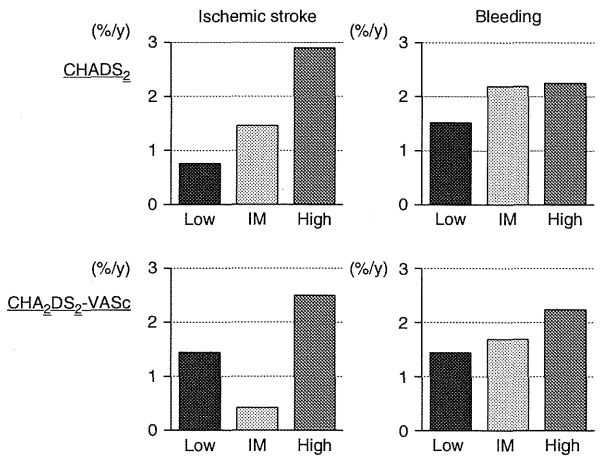

Figure 1 Annual incidence of ischemic stroke and bleeding events by $CHADS_2$ and CHA_2DS_2-VASc scores. Low, score of 0; IM (intermediate), score of 1; high, score of ⩾2.

DISCUSSION

The major finding of the present observational study was that bleeding risk increased gradually as the $CHADS_2$ and CHA_2DS_2-VASc scores increased, although the statistical impact was rather

Table 3 Associations of the components of the CHA_2DS_2-VASc score with risks of ischemic stroke and bleeding events

	Ischemic stroke		*Bleeding*	
	HR	*95% CI*	*HR*	*95% CI*
Heart failure	0.98	0.23–2.84	1.17	0.34–3.02
Hypertension	1.03	0.54–1.98	0.80	0.42–1.52
65–74 Years old	1.02	0.44–2.53	1.68	0.67–4.78
75 Years old or older	1.60	0.72–3.80	2.31	0.96–6.45*
Diabetes mellitus	1.28	0.62–2.52	1.25	0.57–2.54
Stroke and thromboembolism	1.81	0.93–3.66*	0.98	0.51–1.88
Vascular disease	0.82	0.13–2.89	1.68	0.54–4.33
Women	0.75	0.34–1.55	0.86	0.39–1.76

Abbreviations: CI, confidence interval; HR, hazard ratio.
*$0.05 < P < 0.1$ (L 0.073, R 0.064).
Adjusted for antithrombotic medication, neoplasm, liver cirrhosis, hypercholesterolemia, current smoking and alcohol consumption.

Table 2 Associations of $CHADS_2$ and CHA_2DS_2-VASc scores with risks of ischemic stroke and bleeding events

	Ischemic stroke: model 1			*Ischemic stroke: model 2*			*Bleeding: model 1*			*Bleeding: model 2*		
	HR	*95% CI*	P-*values*	*HR*	*95% CI*	P-*values*	*HR*	*95% CI*	P-*values*	*HR*	*95% CI*	P-*values*
$CHADS_2$												
Per 1 −category increase	1.76	1.04–3.38	0.033	1.76	1.03–3.38	0.037	1.10	0.71–1.80	0.679	1.12	0.72–1.84	0.623
Per 1 −point increase	1.35	1.05–1.74	0.019	1.33	1.03–1.73	0.025	1.04	0.81–1.32	0.776	1.05	0.82–1.34	0.717
CHA_2DS_2-VASc												
Per 1 −category increase	2.20	0.91–8.46	0.087	2.18	0.89–8.43	0.096	1.20	0.63–2.85	0.622	1.17	0.61–2.82	0.668
Per 1 −point increase	1.23	1.01–1.51	0.043	1.21	0.99–1.49	0.059	1.10	0.90–1.34	0.362	1.11	0.90–1.36	0.328

Abbreviations: CI, confidence interval; HR, hazard ratio.
Model 1: adjusted for antithrombotic medication.
Model 2: adjusted for antithrombotic medication, neoplasm, liver cirrhosis, hypercholesterolemia, current smoking and alcohol consumption.

weak as compared with their predictive power for ischemic stroke.

The association of bleeding risk with the $CHADS_2$ score for antiplatelet users and anticoagulant users was determined using the cohort of ACTIVE-W,[10] where patients with a score of 0 did not develop major bleeding and those with a score of 1 had a lower incidence of bleeding than those with higher scores. The incidence for intracranial hemorrhage increased as the $CHADS_2$ and CHA_2DS_2-VASc scores increased in patients treated with either warfarin, dabigatran, rivaroxaban or apixaban.[11] In the present study, a similar tendency was seen in Japanese antithrombotic users with AF. A different finding from that of ACTIVE-W was that the annual incidence of major bleeding in patients with the $CHADS_2$/CHA_2DS_2-VASc scores of 0 exceeded 1% per year; it suggests more careful consideration for antithrombotic use in Japanese patients, a known race for high incidence of intracerebral hemorrhage,[12] with the low ischemic risk category than Western patients.

A history of ischemic stroke is a known risk factor for intracerebral hemorrhage.[6,13] Hypertension does not only trigger arteriosclerosis and cause ischemic stroke but also triggers arterial damage and cause bleeding.[14] Aging is another risk factor for both ischemia and bleeding. Thus, ischemic events and bleeding events seem to share many risk factors. To prevent bleeding complications for antithrombotic users, it is essential to choose appropriate numbers and dosages of antithrombotic agents, as well as to avoid elevation of blood pressure and lower it adequately.[7]

The strengths of the study include the multicenter, prospective study design with about 2000 patient-years of follow-up. The limitations of the study include the lack of data about bleeding history and genetic factors in the database to calculate HEMOR-R_2HAGES and HAS-BLED. In addition, the small number of patients in the low ischemic risk category, as well as the relatively low incidences of ischemic stroke and bleeding events, might affect the statistical results. Another potential limitation is heterogeneity of the subjects registered in the BAT study. In particular, patients with different antithrombotic medication seemed to have different clinical backgrounds. However, it was statistically inappropriate to analyze patients separately according to the antithrombotic medication due to small sample size. Finally, the INR levels when the events occurred were not fully collectable.

In conclusion, in Japanese antithrombotic users, bleeding risk increased gradually as the $CHADS_2$ and CHA_2DS_2-VASc scores increased, although the statistical impact was relatively weak. The annual incidence of major bleeding in Japanese antithrombotic users with the $CHADS_2$/CHA_2DS_2-VASc scores of 0 exceeded 1% per year.

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APPENDIX

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Factors Associated with Proximal Carotid Axis Occlusion in Patients with Acute Stroke and Atrial Fibrillation

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Background: Patients with atrial fibrillation (AF) are more likely to exhibit proximal carotid axis occlusion than those without AF. However, clinical characteristics associated with proximal arterial occlusion (PAO) in acute stroke patients with AF are not fully known. This study was aimed to elucidate the factors correlated with PAO. *Methods:* Consecutive patients with acute ischemic stroke developed in the middle cerebral artery (MCA) territory and AF who underwent magnetic resonance angiography (MRA) within 24 h from onset were retrospectively enrolled. Prior users of warfarin were excluded. Patients were divided into 3 groups based on the site of arterial occlusion: occlusion at the internal carotid artery (ICA), at the horizontal segment of the MCA (M1), and at the MCA branch or no identifiable occlusion. Clinical characteristics were compared between the 3 groups, and the factors associated with proximal vessel occlusion were evaluated with ordinal logistic regression analysis. All variables identified on univariable analyses with *P* values less than .1 were entered into the model. *Results:* A total of 244 patients (124 women, median 80 years old [interquartile range 72-87], median National Institutes of Health Stroke Scale [NIHSS] score 16 [7-22]) were studied. MRA was performed median 2.7 h (1.5-8.9) after stroke onset. Occlusion site was the ICA in 34 patients, M1 in 78, and MCA branch or no occlusion in the remaining 132. As the occlusion site was more proximal, patients were older and more female, the initial NIHSS score was higher, levels of D-dimer and brain natriuretic peptide (BNP) were higher, and histories of heart failure and systemic embolism were more common. On multivariable ordinal logistic regression analysis, female sex (odds ratio [OR] 1.83, 95% confidence interval [CI] 1.03-3.26), advanced age (OR 1.37, 95% CI 1.02-1.84 for every 10 years), history of systemic embolism (OR 14.9, 95% CI 1.41-157.75), and higher BNP level (OR 1.03, 95% CI 1.01-1.07 for every 100 pg/mL) were independent factors associated with the risk of occlusion at more proximal arteries. The risk was 2.68-fold higher (95% CI 1.28-5.61) in patients having 2 of the following factors: female sex, age more than 80 years, systemic embolism, and BNP greater than 250 pg/mL; and 4.50-fold (2.11-9.59) higher in those having 3 or 4 of the 4 factors compared with those without any of these factors. *Conclusions:* Female sex, advanced age, history of systemic embolism, and higher BNP level were independently associated with more proximal carotid axis occlusion. Patients with AF having

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Disclosures None.

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these factors may be prone to have relatively large thrombi in the heart. **Key Words:** Acute ischemic stroke—magnetic resonance angiography—atrial fibrillation—arterial occlusion.

Introduction

The site of arterial occlusion plays a key role in neurologic severity and outcome in patients with acute ischemic stroke. Patients with proximal arterial occlusion (PAO) show more severe symptoms,[1,2] poorer outcomes,[3] and more limited response to intravenous tissue plasminogen activator therapy than those with distal artery occlusion.[4,5] The factors associated with PAO are not fully known, and related factors are considered to differ according to the etiologies. Embolic PAO seems to be correlated with embolus size. Patients with atrial fibrillation (AF) often develop severe ischemic stroke and poor outcomes,[6,7] even after thrombolytic therapy,[8] mainly because they are more likely to have PAO on admission than patients without AF.[8] However, clinical factors associated with PAO in patients with AF are not well known.

The aim of this study was to clarify the clinical characteristics related to PAO in acute stroke patients with AF.

Methods

A prospective database of consecutive patients with acute stroke treated in the Stroke Care Unit in the National Cerebral and Cardiovascular Center was created (National Cerebral and Cardiovascular Center Stroke Registry).[9] From April 2006 to May 2012, consecutive acute stroke patients (<24 h from onset) with AF who fulfilled the following criteria were retrospectively enrolled from the registry: (1) underwent magnetic resonance imaging (MRI) examinations including diffusion-weighted imaging (DWI) and time-of-flight magnetic resonance angiography (MRA) on admission and (2) developed ischemic stroke in the middle cerebral artery (MCA) territory confirmed on initial DWI with compatible acute neurologic deficits. Patients with contraindications to MRI (eg, cardiac pacemakers or mechanical heart valve replacements) were excluded. Stroke patients having concomitant etiology other than AF (eg, >50% stenosis on the responsible artery) and patients on anticoagulant therapy were also excluded because anticoagulant therapy could reduce intracardiac thrombi and then affect the site of arterial occlusion in subjects with AF.[10] The institutional ethics committee approved this study.

Clinical Background Characteristics

Clinical background characteristics, including sex, age, cardiovascular risk factors, and medical history, were obtained on admission. Cardiovascular risk factors were defined as: (1) hypertension, history of using antihypertensive agents, systolic blood pressure of 140 mm Hg or more, or diastolic blood pressure of 90 mm Hg or more before or 2 or more weeks after stroke onset; (2) diabetes mellitus, use of hypoglycemic agents, random glucose level of 200 mg/dL or more, or glycosylated hemoglobin of 6.5% or more on admission; (3) hyperlipidemia, use of antihyperlipidemic agents, or a serum total cholesterol level of 220 mg/dL or more; and (4) current smoking habit. Routine blood biochemistry examinations were performed on admission. Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS), and functional outcome was estimated by the modified Rankin scale[11] score at hospital discharge or 30 days from onset. AF was diagnosed on 12-lead electrocardiogram or a history of AF was confirmed.

Neuroimaging

MRI studies including DWI and time-of-flight MRA were performed on admission using a commercially available echo planar instrument operating at 1.5 T (Siemens MAGNETOM Vision or MAGNETOM Sonata scanner, Erlangen, Germany). DWI was obtained using the following parameters: repetition time/echo time, 4000/100 ms; *b* values, 0 and 1000 s/mm^2; field of view, 24 cm; acquisition matrix, 96 × 128; and slice thickness, 4.0 mm, with a 1.0-mm intersection gap. The occluded vessel was determined on initial MRA. All patients were divided into 3 groups based on the occluded site: at the internal carotid artery (ICA) group, at the MCA horizontal segment (M1 group), and at the MCA branch occlusion or no identifiable occlusion (Branch group).

Statistical Analysis

First, clinical background characteristics were compared among the 3 groups. Univariable analyses were performed using the chi-square test, Fisher exact test, or the Kruskal–Wallis test, as appropriate. The data are presented as median values (interquartile range) or frequencies (%). Next, multivariable ordinal logistic regression analysis was performed to identify independent factors associated with more proximal arterial occlusion. This model allows the outcome variable to have more than 2 categories and estimates a proportional odds ratio (OR) for each predictor of shifting to a more proximal arterial occlusion category (eg, the ICA group versus the M1 and Distal groups or the ICA and M1 groups versus the Distal group). Sex, age, and all clinical characteristics identified on univariable analyses with *P* values less

than .1 were entered into the model. Receiver operating characteristic (ROC) curve analyses were conducted to obtain the practical cutoff value of continuous variables. All statistical analyses were performed using PASW for Windows version 17.0 software (SPSS Inc., Chicago, IL). Results were considered significant at P less than .05.

Results

Overall, 503 patients with both acute ischemic stroke and AF were admitted to our stroke center during the study period. Of these, 61 patients were excluded because of absent or incomplete MRI, 29 were excluded because the site of the index stroke was outside the MCA territory, 14 were excluded because of concomitant etiology, and 155 were excluded for taking prestroke anticoagulant therapy. Finally, 244 patients (124 women, median age 80 [interquartile range 72-87] years, median NIHSS score 16 [7-22]) were enrolled in the present study.

Table 1 shows the clinical background characteristics of the included patients. MRA was performed median 2.7 h (1.5-8.9) after stroke onset. Of the 244 patients, 34 (14%) had ICA occlusion (ICA group), 78 (32%) had M1 occlusion (M1 group), and 132 (54%) had MCA branch occlusion or no arterial occlusion (Branch group) on initial MRA. As the occlusion site was more proximal, patients were older ($P < .001$), the initial NIHSS score was higher ($P < .001$), levels of D-dimer ($P = .002$) and brain natriuretic peptide (BNP, $P = .029$) were higher, and female sex ($P = .004$) and histories of heart failure ($P = .047$) and systemic embolism ($P = .001$) were more common.

The results of multivariable ordinal logistic regression analysis are shown in Table 2. Female sex (OR 1.83, 95% confidence interval [CI] 1.03-3.26, $P = .039$), advanced age (OR 1.37, 95% CI 1.02-1.84, $P = .037$ for every 10 years), history of systemic embolism (OR 14.9, 95% CI 1.41-157.75, $P = .025$), and higher BNP level (OR 1.03, 95% CI 1.01-1.07, $P = .048$ for every 100 pg/mL) were independent factors associated with increased risk of more proximal arterial occlusion. The practical cutoff values for age and BNP to predict ICA or M1 occlusion were 80 years (sensitivity, 57%; specificity, 64%; area under the ROC curve, .645) and 250 pg/mL (sensitivity, 57%; specificity, 61%; area under the ROC curve, .578), respectively. Having more of the following 4 factors, female sex, age more than 80 years, history of systemic embolism, and BNP greater than 250 pg/mL was also independently related to more proximal arterial occlusion ($P = .001$, chi-square test, Fig 1). The risk of more proximal arterial occlusion was 2.68-fold higher (95% CI 1.28-5.61) in patients having

Table 1. *Clinical background characteristics*

Variables	Total, n = 244	ICA group, n = 34	M1 group, n = 78	Distal group, n = 132	P
Female sex, n (%)	124 (51)	24 (71)	45 (58)	55 (42)	.004
Age, y, median (IQR)	80 (72-87)	85 (74-88)	82 (74-89)	79 (69-84)	<.001
Onset to MRI, h, median (IQR)	2.7 (1.5-8.9)	2.3 (1.7-6.6)	2.4 (1.4-4.8)	3.8 (1.6-11.4)	.193
Vascular risk factors, n (%)					
Hypertension	171 (70)	24 (71)	52 (68)	95 (72)	.794
Diabetes mellitus	34 (14)	4 (12)	8 (10)	22 (17)	.400
Hyperlipidemia	62 (25)	8 (24)	18 (23)	36 (27)	.768
Current smoking	43 (18)	5 (15)	10 (13)	28 (21)	.286
History, n (%)					
Ischemic stroke	53 (22)	8 (24)	16 (21)	29 (22)	.934
Hemorrhagic stroke	10 (4)	1 (3)	2 (3)	7 (5)	.586
Ischemic heart disease	21 (9)	4 (12)	7 (9)	10 (8)	.732
Heart failure	44 (18)	10 (29)	17 (22)	17 (13)	.047
Peripheral artery disease	10 (4)	2 (6)	2 (3)	6 (5)	.662
Systemic embolism	4 (2)	3 (9)	1 (1)	0 (0)	.001
Prior antiplatelet therapy, n (%)	99 (41)	12 (35)	29 (37)	58 (44)	.500
Initial NIHSS score, median (IQR)	16 (7-22)	22 (18-26)	18 (16-23)	10 (4-17)	<.001
Biochemistry sign at admission, median (IQR)					
Leukocyte count, /μL	6700 (5400-8900)	6700 (4800-9300)	7100 (5600-8600)	6400 (5500-8900)	.580
Blood glucose, mg/dL	124 (107-152)	126 (109-152)	129 (109-152)	119 (106-153)	.467
Total cholesterol, mg/dL	182 (161-206)	172 (164-202)	176 (155-204)	186 (167-211)	.191
D-dimer, μg/mL	2.1 (1.4-3.3)	2.6 (2.0-3.1)	2.1 (1.4-3.5)	1.8 (1.2-3.3)	.002
Brain natriuretic peptide, pg/mL	236 (127-437)	340 (197-666)	266 (130-409)	215 (104-409)	.029

Abbreviations: Distal group: patients with more distal occlusion or no identifiable occlusion; ICA group: patients with internal carotid artery occlusion; IQR, interquartile region; M1 group: patients with middle cerebral artery horizontal segment occlusion; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale.

Table 2. *Result of multivariate ordinal logistic regression analysis for factors associated with larger vessel occlusion*

Variables	OR	95% CI	*P*
Female sex	1.83	1.03-3.26	.039
Age (for every 10 y)	1.37	1.02-1.84	.037
History of heart failure	1.11	.54-2.28	.773
History of systemic embolism	14.9	1.41-158	.025
D-dimer (for every 1.0 μg/mL)	1.01	.91-1.11	.887
BNP (for every 100 pg/mL)	1.03	1.01-1.07	.048

Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval; OR, odds ratio.

2 of the above 4 factors, and 4.50-fold (95% CI 2.11-9.59) higher in those with 3 or 4 of the 4 factors compared with those without any of these factors on ordinal logistic regression analysis (Fig 2).

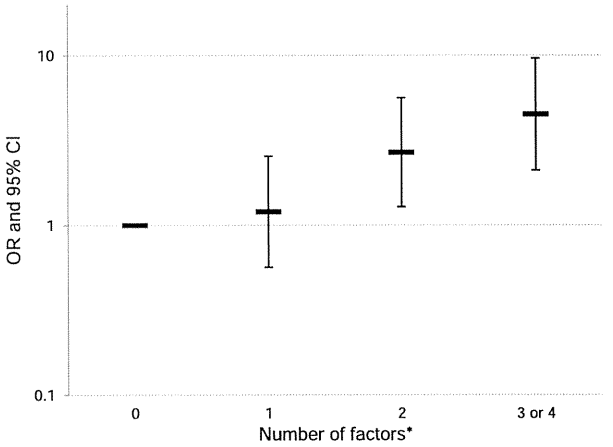

Figure 2. *OR and 95% CI of the risk of more proximal arterial occlusion according to the number of factors independently associated with larger arterial occlusion on ordinal logistic regression analysis. Abbreviations: BNP, brain natriuretic peptide; CI, confidence interval; OR, odds ratio. "*," Female sex, age more than 80 years, history of systemic embolism, and BNP greater than 250 pg/mL.*

Discussion

The first major finding of the present study was that 46% of the patients with both acute ischemic stroke and AF without prior anticoagulant therapy had ICA or M1 occlusion on initial MRA. This percentage was between that of patients within 3 h from onset (75%)[8] and that of patients within 7 days from onset (33%)[12] because the percentage decreases with spontaneous recanalization as onset-to-imaging time increases.[13]

The second major finding was that female sex, advanced age, history of systemic embolism, and higher BNP level were independent factors associated with the risk of more proximal arterial occlusion. In addition, coexistence of 2 or more of these 4 factors clearly increased the risk. This finding is partly in line with the previous reports that showed that advanced age,[14-16] history of systemic embolism,[17] and elevated BNP level[18] were correlated with the presence of intracardiac thrombi in AF patients. However, there is no study investigating the relationships between intracardiac clot size and patients' characteristics. It is possible that a prothrombotic state and large intracardiac thrombi are induced by these factors and cause PAO.

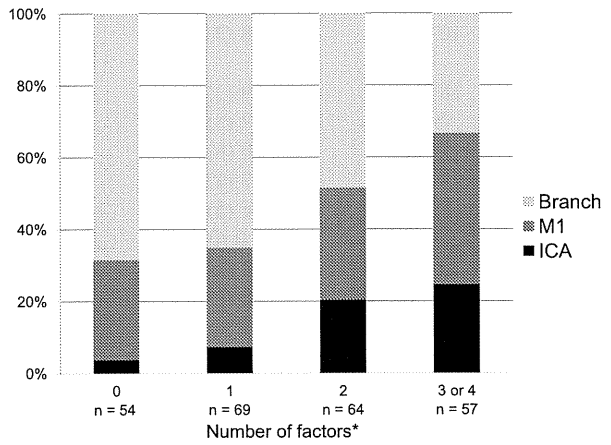

Figure 1. *The site of arterial occlusion based on the number of factors independently associated with larger arterial occlusion. Abbreviations: BNP, brain natriuretic peptide; Branch, middle cerebral artery branch or no identifiable occlusion; ICA, internal carotid artery; M1, middle cerebral artery horizontal segment. "*," Female sex, age more than 80 years, history of systemic embolism, and BNP greater than 250 pg/mL.*

The female hormone, estrogen, increases fibrinolytic potential[19] and accelerates the recovery of injured endothelial cells.[20] Estrogen production is reduced after menopause, and elderly women with AF have a higher clot formation marker level[21] and worse outcomes after stroke[12] than men. Most women in the present study were considered to be postmenopausal because the median age of the included women was 84 years.

Advanced age may represent a longer period with a pathologic condition, such as hypertension, heart failure, and AF. Prolonged exposure to these pathologic conditions leads to cardiac remodeling, including left atrial enlargement and reduced atrial contractility.[22-24] This remodeling causes blood stasis in the left atrium and left atrial appendage and could contribute to form large thrombi. Furthermore, advanced age itself may be associated with a prothrombotic state.[25]

BNP is proven to be well correlated with heart failure,[26] though a high BNP level remained an independent predictor for PAO in the present patients using the regression model containing both heart failure and BNP as variables. The association of BNP with PAO independently from heart failure was because a high BNP level also stands for high left ventricular filling pressure,[27] which leads to left atrial enlargement[28] and left atrial appendage dysfunction[29]; all these cause formation of large thrombi. A history of systemic embolism may also indicate that the patients were prothrombotic.

This study had some limitations. First, the retrospective design might have contributed to some selection bias. Second, PAO might be overestimated because distal arterial occlusion and slow flow velocity in the proximal arteries are sometimes difficult to distinguish from PAO on MRA. On the other hand, the inclusion criteria of less than 24 h of onset might lead underestimation of the presence of PAO because of spontaneous recanalization, despite the MRI examinations were performed 2.7 h (median) from onset in the present study. Third, only the internal validity of the present results was assessed. The present findings should be confirmed with a prospective cohort.

In conclusion, nearly half of acute stroke patients with AF who did not receive anticoagulant therapy had ICA or MCA horizontal segment occlusion. Female sex, advanced age, history of systemic embolism, and higher BNP level were independent factors associated with PAO. Patients having these factors may be prone to having larger thrombi in the heart than those without these factors.

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