3 頸動脈病変の評価 —プラークの分類・プラークスコア

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A プラークの分類

プラークは，エコー輝度，表面性状，均一性，可動性の4項目から分類できる．

1．エコー輝度

エコー輝度からは，低輝度（hypo echoic, low echoic），等輝度（iso echoic, echogenic），高輝度（hyper echoic, calcified）の3群に分けられることが多い（**図1**）．それぞれの輝度の目安は，低輝度は血液に近い輝度，等輝度は周囲の筋肉や内中膜複合体，高輝度は骨を対照としている．これらの輝度分類は病理組織と対応しているとされており，低輝度は粥腫や血腫，等輝度は線維性病変，高輝度は石灰化と対応しているといわれている．そのため低輝度プラークは脆弱であるため，脳梗塞発症の危険性が高いと考えられており，それを支持する報告も多い[1,2]．一方，無症候性の頸動脈病変ではエコー輝度と脳梗塞発症率に差がないとする報告もある[1]．低輝度プラークは確かに病理所見の粥腫に合致するが，等輝度プラークはすべてが線維性病変のみで構成されているわけではなく，プラークの破綻を繰り返した結果，線維成分が増加したプラークも含まれているので等輝度であるから必ずしも安定したプラークとはいえない（**図2**）．

エコー輝度で一番の問題点は，客観的な評価ではないということである．検者が経験に頼り分類しているため，検者間で判定に大きな差がある．また機器の設定でエコー輝度は変化するし，機種によっても見え方は大きく異なることもある．少なくとも対象物と比較するためには輝度の定量化が不可欠である．最近では市販のコンピュータソフトを用いてgray scale medianという定量値を計測する方法も普及している[3]（**図3**）．さらに超音波の生信号を解析し，元の信号に含まれる情報をすべて利用し，機種による差をなくす方法も試みられている．これはintegrated backscatterという方法で[4]（**図4**），肝臓や心筋にも用いられている．しかし現時点ではいずれの方法も煩雑で，日常検査で使っていくことは困難である．将来診断装置に組み込まれ，ボタン一つで定量化できる機能が期待される．

2．表面性状

表面性状はその臨床的意義がもっとも検討されているのは潰瘍である．潰瘍の定義は深さ2mm以上という基準が多く用いられてきているが，診断機器の性能が上がり2mm以下の潰瘍も十分検出できるようになっている（**図5**）．潰瘍はプラークの破綻により生じるものなので，プラークが脆弱であることの証明となる．潰瘍が存在すると脳梗塞の発症率が上がるとする報告も多い[5]．

表面性状からは潰瘍と平滑の間に，不整という表現がある．血管撮影などで用いられる壁不整にあたるものであるが，臨床的意義についてはまだ報告が少なく，定義も曖昧である．

3．均一性

いろいろなエコー輝度の部分が混在する不均一なプラークは，病理組織上でも粥腫，線維成分，石灰化病変で複雑に構成されている．不均一なプラークは同じ狭窄率でも症候性の病変であることが多いとの報告もあり[6]，より脆弱なプラークと考えられている．

4．可動性

超音波検査はreal timeに動きがみえるという，ほかの検査にはない長所がある．これまで浮遊血栓がプラークに付着した症例が報告されている．

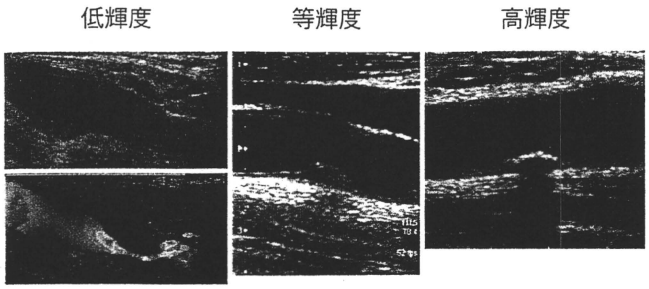

図1　プラークの輝度分類

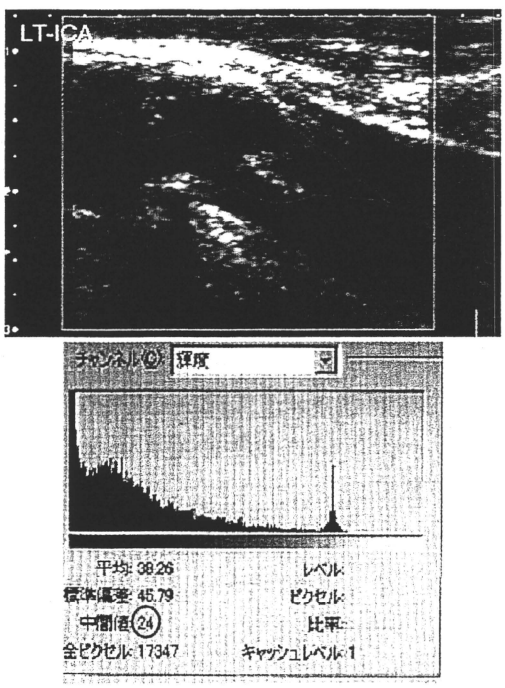

図3　gray scale median の計測

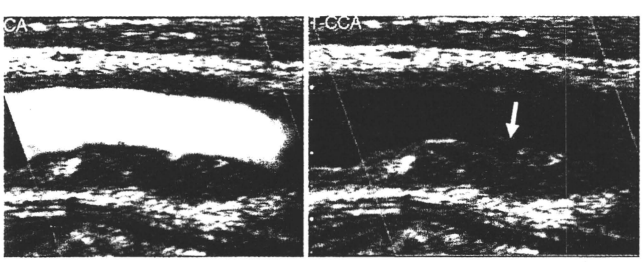

図5　小さな潰瘍
深さは 2 mm 以下であるが，確実に潰瘍と思われる所見がみられる．

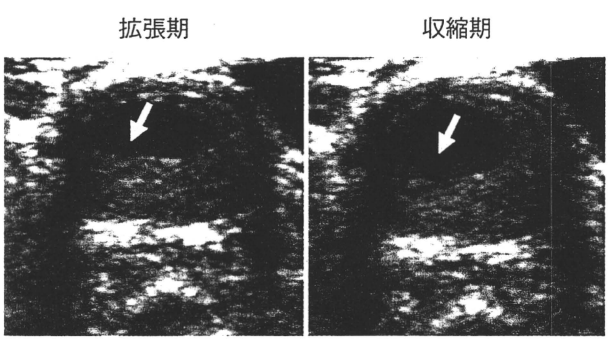

図6　可動性プラーク
プラークの一部に可動性が認められる．

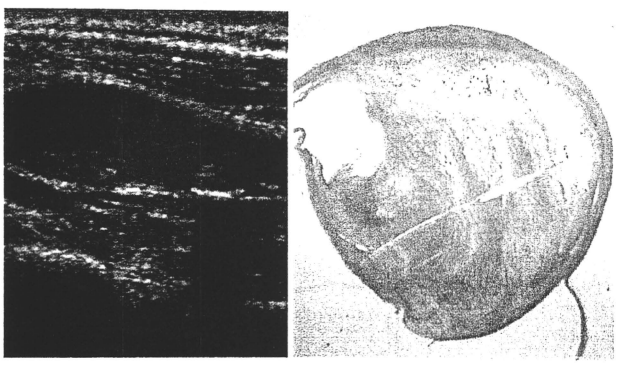

図2　等輝度プラークと病理組織
粥腫と線維性病変が交互に並び，プラーク破綻を繰り返していることが示唆される．

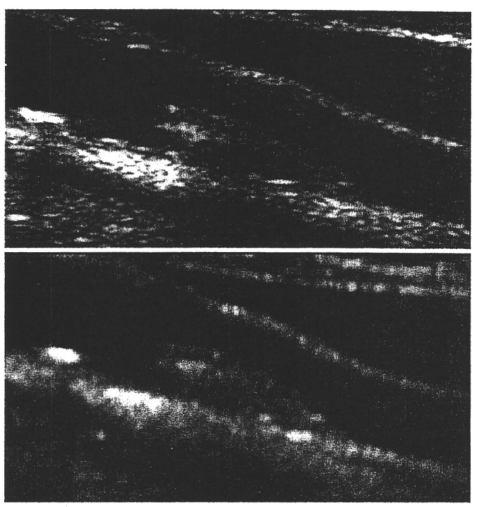

図4　B モード画像と integrated backscatter（IBS）画像
IBS 画像は超音波の生信号から構築されており，画像として鮮明でないが，信号処理による情報の変化がない．

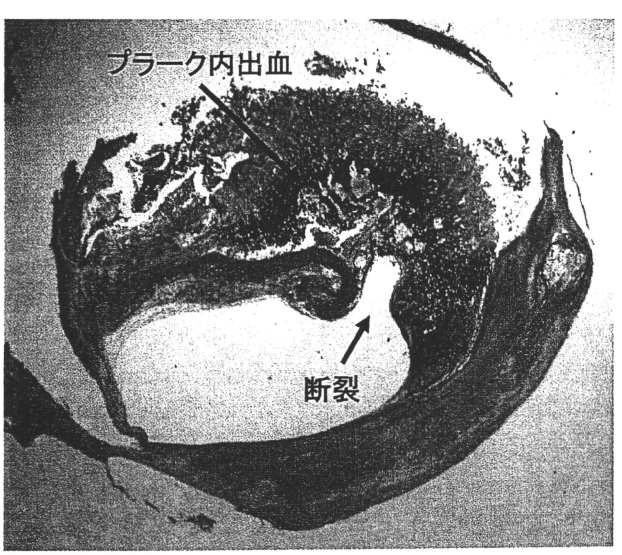

図7　図6の病理組織
プラークの破綻と新鮮なプラーク内出血を認める．

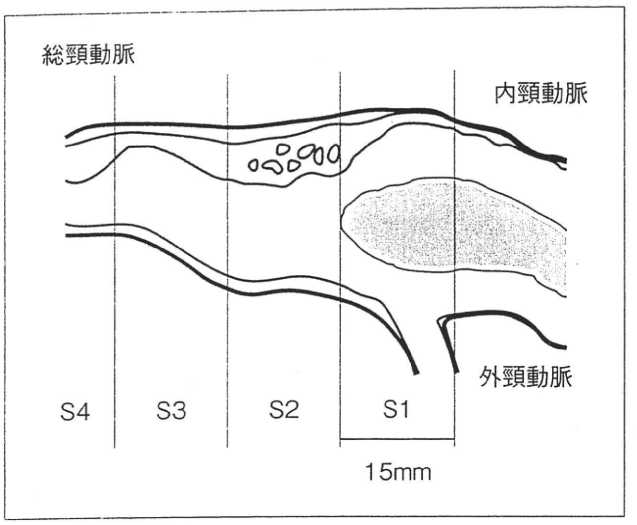

図8　プラークスコア

確かにリスクの高い重要な所見であるが，あまり頻度も高くはないため注目はされていない．最近診断機器の進歩により詳細な画像が得られるようになり，プラークの一部に可動部分が認められるものが見つかるようになった（**図6**）．このような可動性プラークの病理標本をみるとプラークの破綻や新鮮なプラーク内出血が高頻度でみられ（**図7**），特に症候性の病変では進行や再発する例が多いので注意が必要である．

B プラークスコア

プラークスコアはHandaら[7]が提唱したパラメーターで，プラークの大きさと数を同時に評価できる点で優れている．プラークスコアは**図8**に示すように頸動脈を1.5 cm間隔で4分割し，プラークの高さを左右合計したものである．進行した粥状硬化のパラメーターとして用いられている．プラークスコアが1.1～5.0を軽度動脈硬化，5.1～10.0を中等度動脈硬化，10.1以上を高度動脈硬化としている．プラークスコアが脳卒中の病型により異なること，プラークスコアが大きいと脳梗塞の発症頻度が高いこと，高感度CRPが高い群でプラークスコアの年間増加率が高いことなどが報告されている．

Silent Cerebral Infarcts and Cerebral White Matter Lesions in Patients with Nonvalvular Atrial Fibrillation

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Background: Nonvalvular atrial fibrillation (NVAF) is a well-known strong risk factor for stroke, although few studies have examined silent cerebral ischemic lesions in patients with NVAF. We investigated silent cerebral infarcts (SCIs) and cerebral white matter lesions and risk factors for stroke in NVAF patients. *Methods:* Subjects included 71 consecutive patients with NVAF and 71 sex-and age-matched controls with sinus rhythm who had undergone MRI. Number, size, and localization of SCIs and severity of periventricular hyperintensity (PVH) and deep and subcortical white matter hyperintensity (DSWMH) on magnetic resonance imaging were analyzed. The risk factors and CHADS2 score for stroke were also investigated. *Results:* The number of SCIs was significantly larger and the rates of SCIs in the cortex/subcortex and deep white matter were higher in the NVAF group than in the control group. The DSWMH grade was also significantly higher in the NVAF group. NVAF was an independent risk factor for SCIs and DSWMH. The number of cortical and subcortical SCIs was significantly correlated with CHADS2 score. *Conclusions:* Cortical/subcortical and deep white matter SCIs were more frequent and DSWMH grades were higher in NVAF patients compared with control subjects. CHADS2 score was an effective scheme not only in stroke risk but also in risk of SCI. **Key Words:** Atrial fibrillation—silent brain infarction—cerebral white matter lesion—maginetic resonance imaging.

Silent cerebral infarcts (SCIs) and cerebral white matter lesions with no obvious neurologic symptoms appear from middle age onward, and their frequency tends to increase with advancing age.[1] Both types of lesion, if present in large numbers, have been shown to result in progressive decline of cognitive function[2,3] and psychological symptoms, such as depression.[4] A high probability of future stroke has also been reported in individuals with these lesions.[5]

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A pathologic study in Hisayama, Japan showed that SCIs are frequently observed in the subcortex, and that age, hypertension, and atrial fibrillation are significant risk factors for SCIs.[6] Cerebral white matter lesions are categorized into periventricular hyperintensity (PVH) and deep and subcortical white matter hyperintensity (DSWMH). Age[7] and hypertension[8] have previously been identified as risk factors for these lesions, and they are also believed to be the result of impairment in the cerebral arterioles.[9]

There have been several previous reports of research on nonvalvular atrial fibrillation (NVAF) and SCIs, and it has been reported that not only cerebral embolism but also SCIs are likely to occur in NVAF patients,[10,11] although only few studies have addressed the relationship of NVAF with SCIs and cerebral white matter lesions. In this study, we investigated the characteristics of cerebral white matter lesions without neurologic symptoms and SCIs on magnetic resonance imaging (MRI) and also investigated the relationship of these lesions with risk

factors for stroke in NVAF patients and non-NVAF patient controls.

The CHADS2 score is widely used for risk stratification in NVAF patients; the score includes *c*ongestive heart failure, *h*ypertension, *a*ge over 75 years, *d*iabetes mellitus, and history of *s*troke or transient ischemic attack (TIA) as risk factors for stroke.[12,13] However, the usefulness of the scheme in Japanese patients has not been adequately clarified. In our study, the association of CHADS2 score with SCIs in NVAF patients was also examined.

Methods

The subjects were patients who had attended or were admitted to our hospital between 2003 and 2007. All patients in our study had undergone cranial MRI.

The NVAF group consisted of 71 consecutive patients (48 males, 23 females; average age, 74.4 ± 9.9 years) with chronic atrial fibrillation (29 patients) or documented paroxysmal atrial fibrillation (42 patients), excluding those with atrial fibrillation associated with valvular disease.

The control group consisted of 71 consecutively sex- and age-matched patients (48 males, 23 females; average age, 73.7 ± 8.2 years) with sinus rhythm who had been examined in our department during the same period and who did not have any central nervous system involvements.

No patients in either group had a history of stroke or TIA, and patients with known neurologic disorders were excluded. The control group did include patients with subjective symptoms alone, such as headache, dizziness, tinnitus, and tingling of the hands or feet.

MRI was performed using a 1.5-T system device that visualized T1- or T2-weighted MRI images in 7-mm slices with gaps of 0.50 mm parallel to the orbitomeatal (OM) line. MRI was conducted according to the following conditions: standard axial T1 (TR, 425-510 ms; TE, 12-13ms), standard axial T2 (TR, 3000-3247 ms; TE, 90-122 ms), with a field of view 220 × 220. Scattered, irregularly shaped lesions of diameter ≥3 mm presenting as T2 high-intensity and T1 low-intensity findings on horizontal sections were regarded as SCIs. Lesions <3 mm were excluded because there was a high possibility to include dilatation of the perivascular space, demyelination, or gliosis.[14]

Previous reports have stated that among subcortical small infarcts, cerebral infarcts with a diameter ≥5 mm are more likely to be associated with atherosclerosis of major arteries and platelet activation than those with a diameter <5 mm.[15] Therefore, in this study, the size of the infarct area was classified as either 3 to 5 mm or >5 mm. The number of SCIs was classified into 1 of 3 categories: "0," "1-2," or "≥3." Localization of ischemic lesions visible on MRI was classified into 1 of the following 5 categories: cortex/subcortex, deep white matter, thalamus/basal ganglia, brain stem, and cerebellum.

Cerebral white matter lesions were classified into PVH and DSWMH according to the classification of Fazekas.[16] PVH was categorized as: grade 0, absent; grade 1, caps or pencil-thin lining; grade 2, smooth halo; and grade 3, irregular PVH extending into deep white matter. DSWMH was categorized as: grade 0, absent; grade 1, punctuate foci; grade 2, beginning confluence of foci; and grade 3, large confluent areas.

All images were shuffled before evaluation and interpreted by multiple neurologists and neuroradiologists who were blinded to the clinical data. The final diagnosis of each MRI lesion was made by consensus.

We also investigated the relationships with vascular risk factors (hypertension, hypercholesterolemia, diabetes, cigarette smoking, and alcohol drinking), body mass index (BMI), maximum intima-media thickness (max IMT) of the carotid artery measured by high resolution duplex ultrasonography, left atrial diameter (LAD) measured by transthoracic echocardiography, blood coagulation markers (thrombin-antithrombin III complex [TAT], and D-dimer), platelet activation marker (β-thromboglobulin [β-TG]), which were quantitated using enzyme immunoassay, and the CHADS2 score.

Hypertension was defined as blood pressure ≥140/90 mm Hg, an obvious history of hypertension, or a history of drug treatment. Diabetes was defined as HbA1c ≥6.0%, an obvious history of diabetes, or a history of drug treatment. Hypercholesterolemia was regarded as total serum cholesterol ≥220 mg/dL, an obvious history of hypercholesterolemia, or a history of drug treatment.

Smoking was considered habitual if the patient had a history of smoking at least 20 cigarettes a day for at least 1 year. Drinking was considered habitual if the patient had consumed at least 30 g of alcohol a day for at least 1 year.

The CHADS2 score is a risk stratification system for NVAF patients.[13] Scores of 0 to 6 points are determined based on the following factors: *c*ongestive heart failure (1 point); *h*ypertension (1 point); *a*ge over 75 years (1 point); *d*iabetes mellitus (1 point); and previous *s*troke or TIA (2 points).

Statistical analyses were performed using SAS (version 9.0; SAS Institute; Cary, NC), with $P < .05$ being statistically significant. The Student t and Mann–Whitney U tests were used to compare ages, numbers of SCIs, and test values between the 2 groups, and the Chi-square test was used to compare risk factors with the prevalence of SCIs and cerebral white matter lesions. Age, sex, hypertension, hypercholesterolemia, diabetes, NAVF, and aspirin intake were also analyzed as independent risk factors for MRI lesions using a multiple logistic regression analysis. The association of CHADS2 score with number of SCIs in NVAF patients was examined using the Spearman correlation analysis. Age and test values were all expressed as means ± standard deviations (SD). Differences at $P < .05$ were considered significant for all results.

Table 1. *Baseline characteristics in patients with nonvalvular atrial fibrillation and control subjects*

	n	NVAF	n	Control	*P* value
Age	71	74.4 ± 9.9	71	73.7 ± 8.2	.658*
Chronic AF	29	40.8%	—	—	—
Paroxysmal AF	42	59.2%	—	—	—
Hypertension	45/71	63.4%	41/71	57.7%	.492†
Diabetes mellitus	20/71	28.2%	19/71	26.8%	.851†
Hypercholesterolemia	25/71	35.2%	30/71	42.3%	.389†
Aspirin intake	39/71	54.9%	36/71	50.7%	.614†
Warfarin intake	22/71	31.0%	1/71	1.4%	<.001†
Smoking‡	19/68	27.9%	23/57	40.4%	.144†
Drinking‡	22/63	34.9%	26/53	49.1%	.124†
BMI‡	56	23.5 ± 3.0	54	22.6 ± 3.3	.170*
Max IMT‡	36	2.3 ± 1.0	57	2.1 ± 1.0	.185§
LAD‡	49	3.9 ± 1.0	6	3.3 ± 0.4	.036§
TAT‡	22	1.5 ± 1.0	14	1.4 ± 0.5	.28§
D-dimer‡	21	1.3 ± 4.1	14	0.8 ± 1.2	.34§
β-TG‡	38	39.0 ± 23.1	37	34.1 ± 12.9	.33§

Abbreviations: β-TG, β-thromboglobulin; AF, atrial fibrillation; BMI, body mass index; max IMT, maximum intima-media thickness of carotid artery; LAD, left atrial diameter; TAT, thrombin-antithrombin III complex.

Values are mean ± SD. $P < .05$ was considered statistically significant.

*Differences compared with control subjects using the Student independent *t* test.

†Chi-square test.

‡Subject numbers were different between 2 groups because of missing data. We analyzed only the available data.

§Mann–Whitney *U* test.

Results

Background Characteristics

Background characteristics in the control and NVAF groups are shown in Table 1. The respective frequencies of risk factors in the control and NVAF groups were 57.7% and 63.4% for hypertension, 26.8% and 28.2% for diabetes, and 42.3% and 35.2% for hypercholesterolemia, respectively, with none of the differences being significant. The respective percentages of oral intake of antiplatelet agents in the control and NVAF groups were 50.7% and 54.9%, with no difference observed, but the respective percentages of oral intake of anticoagulants (warfarin) were 1.4% and 31.0%, significantly higher in the NVAF group. There were no differences for smoking, drinking, BMI, and max IMT, but the NVAF group had a significantly higher LAD value. There were no significant differences between the two groups in TAT, D-dimer, or β-TG.

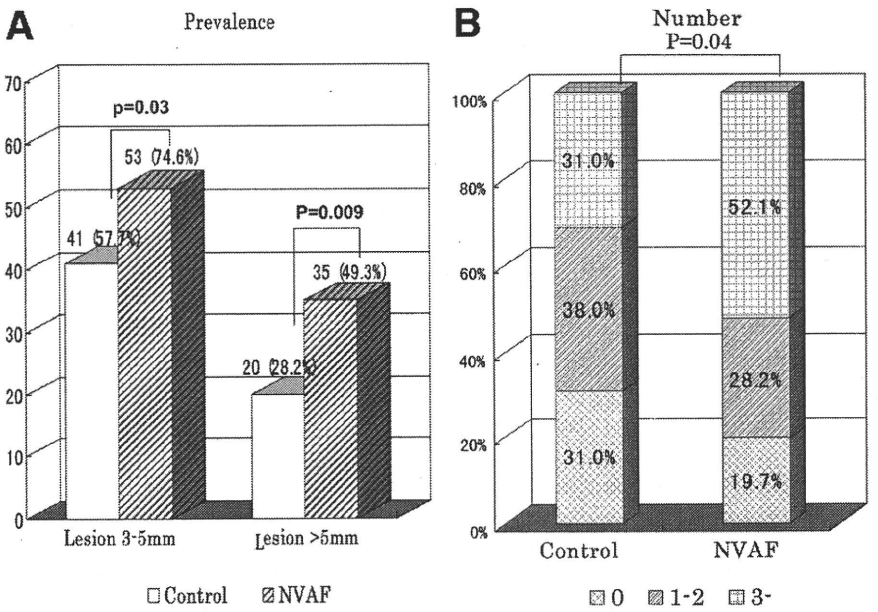

Figure 1. *Prevalence and number of silent cerebral infarction (SCI) by size on magnetic resonance imaging. (A) The percentage of patients with at least 1 SCI with a size of 3 to 5 mm or >5 mm were significantly higher in the nonvalvular atrial fibrillation (NVAF) group (lined columns) than in the control group (open columns). (B) The number of SCIs was also significantly larger in the NVAF group than in the control group. Statistical analysis was performed using the Chi-square test (A) and the Mann–Whitney U test (B).*

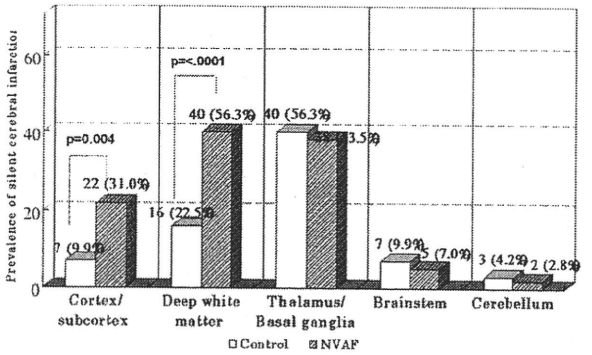

Figure 2. *Location of silent cerebral infarction (SCI) on magnetic resonance imaging. SCIs in the cortex/subcortex and in the deep white matter were more frequent in the nonvalvular atrial fibrillation group (lined columns) than those in the control group (open columns). There were no significant differences in the thalamus/basal ganglia, brainstem, or cerebellum. Statistical analysis was performed using the Chi-square test.*

Cerebral White Matter Lesions

No difference in grade between the control and NVAF groups was seen for PVH, but the DSWMH grade was significantly higher in the NVAF group (Figure 3).

A comparison of the presence or absence of PVH and DSWMH with age and other factors showed that age was significantly higher and hypertension significantly more frequent in patients with PVH, while age was significantly higher and NVAF significantly more frequent in patients with DSWMH (Table 4).

Multiple logistic regression analysis was conducted in the same way as for SCIs to investigate the relationship with risk factors. Age alone was an independent risk factor for PVH, whereas for DSWMH not only age but also NVAF was an independent risk factor (Table 5).

Discussion

In this study, NVAF patients had a higher rate of SCIs than the control patients. In previous studies, the rate of SCIs has been found to be 8% to 28% in healthy individuals[5,17] and 8% to 57% in patients with cardiovascular disease, hypertension, and diabetes mellitus.[17]

In the present study, the percentages of patients in the control group with SCIs from 3 to 5 mm and >5 mm were 57.7% and 28.2%, respectively, while the NVAF group had higher rates (74.6% and 49.9%, respectively). The rate of SCIs was thought to be higher relatively because this study was hospital-based and the subjects were older than those in previous studies.

The NVAF group had also significantly larger number of SCIs than the control group, and high rates of SCIs were observed in the cortex/subcortex and in the deep white matter in patients with NVAF.

Previous research has shown that approximately 80% of microthrombi injected into the carotid artery embolize to gray matter regions.[18] In addition, it has been reported that multiple small infarcts in the cortex seen on MRI diffusion-weighted images are actually embolisms or small embolic fragments.[19,20] From these, high rates of SCIs in the cortex/subcortex in NVAF patients may be small silent cardiogenic embolism to preferentially occur in those with than without NVAF.

On the other hand, it is possible that deep white matter SCIs may reflect in situ small vessel disease. It has previously been reported that the administration of aspirin, which has an antiplatelet effect, resulted in the reduction of deep white matter and basal ganglia SCIs in patients with NVAF, and, because no change was seen in the cortex/subcortex, the authors speculated that SCIs in the deep white matter and basal ganglia region were not

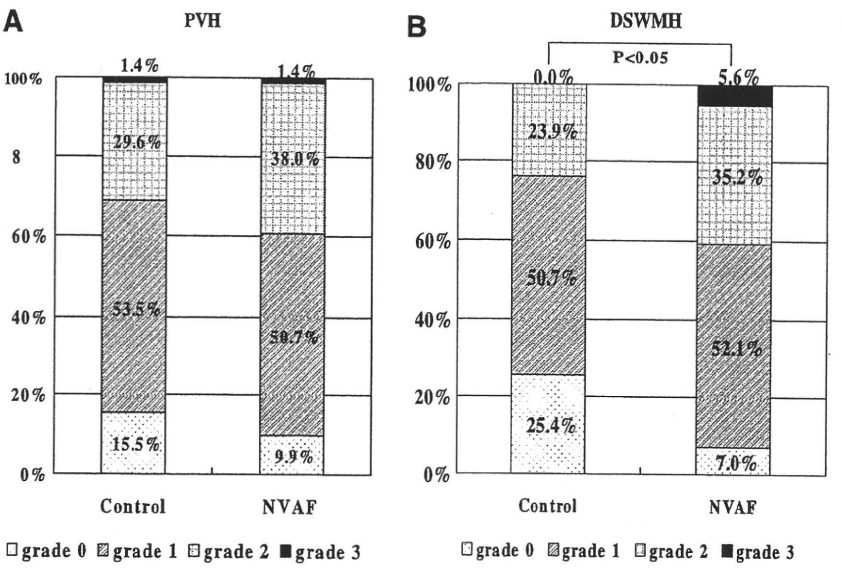

Figure 3. *Prevelance of periventricular hyperintensity (PVH) and deep and subcortical white matter hyperintensity (DSWMH). (A) There was no difference for PVH grade between the control group and the nonvalvular atrial fibrillation (NVAF) group. (B) The DSWMH grade was significantly higher in the NVAF group than in the control group. Statistical analysis was performed using the Chi-square test.*

Table 2. *Prevalence of risk factors for silent cerebral infarction*

	SCI (3-5 mm)					SCI (>5 mm)				
	(-)		(+)			(-)		(+)		
Risk factor	n = 48		n = 94		*P* value	n = 87		n = 55		*P* value
Age <75 y	18	37.5%	52	55.3%	.04	35	40.2%	35	63.6%	<.01
Male	34	70.8%	62	66.0%	.56	61	70.1%	35	63.6%	.42
Hypertension	27	56.3%	59	62.8%	.45	51	58.6%	35	63.6%	.55
Hypercholesterolemia	20	41.7%	35	37.2%	.61	38	43.7%	17	30.9%	.13
Diabetes mellitus	13	27.1%	26	27.7%	.94	24	27.6%	15	27.3%	.97
NVAF	18	37.5%	53	56.4%	.03	36	41.4%	35	63.6%	.01
Aspirin intake	22	45.8%	53	56.4%	.23	49	56.3%	26	47.3%	.29
Warfarin intake	4	8.3%	19	20.2%	.07	10	11.5%	13	23.6%	.06

Abbreviations: NVAF, nonvalvular atrial fibrillation; SCI, silent cerebral infarction.
Differences compared with control subjects by Chi-square test.
Values are mean ± SD.
$P < .05$ was considered statistically significant.

Silent Cerebral Infarcts

The proportions of patients in the NVAF group with at least 1 SCI 3 to 5 mm in size and >5 mm in size were 74.6% and 49.3%, respectively, compared with 57.7% and 28.2%, respectively, for the control group. The positive percentages in both sizes of SCI were significantly higher in the NVAF group than in the control group. The numbers of SCIs were also significantly larger in the NVAF than the control group (Figure 1).

No significant difference between chronic and paroxysmal atrial fibrillation was seen in either the proportion of patients with the presence of SCIs or the numbers of SCIs.

A comparison of the presence or absence of SCIs with age and other factors showed that age and NVAF were significant factors for both 3 to 5 mm and >5 mm sizes of SCIs (Table 2).

Multiple logistic regression analysis was also performed to investigate the relationships between risk factors and SCIs. In this issue, NVAF was observed to be correlated with oral anticoagulant intake, so it was excluded from the factors. The results also showed that age and NVAF were significant factors for both sizes of SCIs (Table 3).

In the NVAF group, 31.0% of SCIs were seen in the cortex/subcortex and 56.3% in the deep white matter, which were more frequent than those in the control group (9.9% in the cortex/subcortex and 22.5% in the deep white matter). On the other hand, there were no significant differences in the thalamus/basal ganglia, brain stem, and cerebellum (Figure 2).

Spearman correlation analysis revealed that CHADS2 scores were associated with the number of SCIs in the cortex/subcortex ($r = 0.277$; 95% confidence interval [CI], 0.05-0.48; $P < .01$). By contrast, in the deep white matter, thalamus/basal ganglia, brain stem, or cerebellum, there was no association with CHADS2 score and the number of SCIs. The CHADS2 score were not assessed by multivariate analysis because the scheme takes age and hypertension into account.

Table 3. *Multiple logistic regression analysis of risk factors for silent cerebral infarction*

	SCI (3-5 mm)			SCI (>5 mm)		
Risk factor	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.07	1.02-1.12	<.01	1.08	1.03-1.13	<.01
Male	0.84	0.37-1.93	.68	0.77	0.35-1.72	.52
Hypertension	0.98	0.46-2.11	.97	0.89	0.41-1.90	.74
Hypercholesterolemia	0.79	0.36-1.71	.54	0.58	0.26-1.27	.17
Diabetes mellitus	0.82	0.35-1.93	.65	0.89	0.38-2.07	.78
NVAF	2.18	1.03-4.61	.04	2.53	1.21-5.30	.01
Aspirin intake	1.61	0.77-3.43	.22	0.68	0.32-1.44	.32

Abbreviations: CI, confidence interval; NVAF, nonvalvular atrial fibrillation; OR, odds ratio; SCI, silent cerebral infarction.
$P < .05$ was considered statistically significant.

Table 4. *Prevalence of risk factors for periventricular hyperintensity and deep and subcortical white matter hyperintensity*

	PVH (%)					DSWMH (%)				
	(-)		(+)			(-)		(+)		
Risk factor	n = 18		n = 124		*P* value	n = 23		n = 119		*P* value
Age >75 y	5	27.8%	65	52.4%	.04	6	26.0%	64	53.8%	.02
Male	14	77.8%	82	66.1%	.32	18	78.3%	78	65.5%	.23
Hypertension	7	38.9%	79	63.7%	.04	10	43.5%	76	63.9%	.06
Hypercholesterolemia	5	27.8%	50	40.3%	.45	8	34.8%	47	39.5%	.67
Diabetes mellitus	1	5.6%	38	30.6%	.05	3	13.0%	36	30.3%	.09
NVAF	7	38.9%	64	51.6%	.31	5	21.7%	66	55.5%	<.01
Aspirin intake	10	55.6%	65	52.4%	.80	10	43.5%	65	54.6%	.32
Warfarin intake	2	11.1%	21	16.9%	.77	2	8.7%	21	17.6%	.44

Abbreviations: DSWMH, deep and subcortical white matter hyperintensity; NVAF, nonvalvular atrial fibrillation; PVH, periventricular hyperintensity.

Values are mean ± SD.

$P < .05$ was considered statistically significant. Differences compared with control subjects using the Chi-square test.

caused by fibrin clots, but rather platelet thrombi probably formed on the deep perforating arteries.[21]

Because deep white matter constitutes the boundary zone for cerebral blood flow, hemodynamic mechanisms give rise to ischemia and to form of secondary thrombi. Caplan and Hennerici[22] have hypothesized that embolism and low perfusion exert a synergistic effect. Low perfusion reduces the blood flow for washing emboli away, while emboli block the blood supply, further worsening ischemia. These suggest that the deep white matter SCIs seen in the NVAF patients were probably the result of a combination of low perfusion caused by hemodynamic mechanisms and microthrombi.

In our results, there was no significant difference in the basal ganglia/thalamus SCIs between the NVAF and control groups. Recent reports indicated that risk factors for the basal ganglia infarcts are different from those for deep white matter infarcts, and carotid artery stenosis and coronary artery disease were significant and independent predictors of the basal ganglia infarcts.[23-25] Therefore, the SCIs in the basal ganglia were more likely to be paralleled with a background systemic atherosclerosis.

Most previous studies showed that hypertension was associated with SCIs, but it was not a significant risk factor in this study. The results showed that age and NVAF but not hypertension was significant factor for SCIs. The reason for this discrepancy between the previous studies and our study was that the hypertension percentage of the subjects in both groups of this study was higher than in the previous studies, and because half of the subjects were NVAF patients. These differences in the proportions of hypertension and NVAF between the previous studies and this study might have affected the results of statistical analysis.

We also found that, compared with the control group, NVAF patients had a significantly higher DSWMH grade,

Table 5. *Multiple logistic regression analysis of risk factors for periventricular hyperintensity and deep and subcortical white matter hyperintensity*

	PVH			DSWMH		
Risk factor	OR	95% CI	*P* value	OR	95% CI	*P* value
Age	1.08	1.01-1.15	.02	1.13	0.83-0.95	<.01
Male	0.54	0.15-1.95	.34	0.43	0.66-8.34	.20
Hypertension	2.01	0.66-6.10	.22	1.69	0.59-4.91	.33
Hypercholesterolemia	1.73	0.52-5.78	.37	1.01	0.33-3.11	.99
Diabetes mellitus	7.28	0.88-60.14	.07	2.58	0.61-10.89	.20
NVAF	1.91	0.62-5.90	.26	7.34	2.04-26.41	<.01
Aspirin intake	0.64	0.21-1.98	.44	1.48	0.51-4.27	.47

Abbreviations: CI, confidence interval; DSWMH, deep and subcortical white matter hyperintensity; NVAF, nonvalvular atrial fibrillation; OR, odds ratio; PVH, periventricular hyperintensity.

$P < .05$ was considered statistically significant.

while there was no difference in the PVH grade. Multiple logistic regression analysis showed that age was a significant independent risk factor for PVH, whereas not only age but also NVAF was a significant independent risk factor for DSWMH. In a comparison of the 2 groups, patients with PVH were significantly older and had a higher frequency of hypertension, a result consistent with previous reports.[7,8]

Pathologically, PVH is associated with other age-related changes, such as pallor of the myelin sheath and expansion of the perivascular space, which manifests on MRI scans as rim, caps, or a smooth halo, although they are not regarded as abnormal findings.[26]

In DSWMH, small infarct areas are mixed with age-related changes, and these are regarded as reflecting atherosclerosis of perforators. They are seen in elderly people with vascular risk factors and are recognized as chronic ischemia.[26,27]

The present study found the frequency of DSWMH to be significantly higher in NVAF patients, suggesting the existence of small artery disease. It has been proposed that for SCIs, the cause lies in the low cerebral perfusion by reduced cardiac output in NVAF patients.[28,29] It has previously been reported that chronically low perfusion affects cerebral white matter lesions[30] and a higher rate of cerebral white matter lesions observed in atrial fibrillation accompanied by left ventricular hypertrophy has also been reported.[28]

According to recent reports, the irregular heartbeat of atrial fibrillation gives rise to turbulence in the blood flow and damages the vascular endothelial cells, reducing production of nitric oxide, which has an antithrombotic effect.[31] It has also been shown that shear stress generated by atrial fibrillation affects the vascular endothelium and inhibits nitric oxide synthesis, and that the nitric oxide synthase inhibitor asymmetric dimethyl arginine increases.[32] Furthermore, there have also been reports on platelet activation in atrial fibrillation as a result of expression of the platelet adhesion molecule P-secretin[33] and blood hypercoagulation in the early stages after atrial fibrillation.[34,35]

From these facts, not only does cerebral blood flow diminish but also antithrombotic action decreases in NVAF patients and these effects may combine to generate a high rate of deep white matter lesions.

The CHADS2 score was an independent prognostic factor for cerebral infarction in NVAF patients as reported.[36] In our study, the number of SCIs in the cortex/subcortex was significantly increased according to the increase of CHADS2 score. Our results revealed that this scoring system was an effective scheme not only in stroke risk but also in risk of SCI.

Conclusions

A high rate of cortical/subcortical and deep white matter SCIs was observed in NVAF patients, and the mechanism for their generation is thought to consist of the synergistic effect of microthrombi and hemodynamic abnormalities. High-grade white matter lesions were also common in NVAF patients, and diminished cerebral blood flow and reduced antithrombotic action may be involved in their pathogenesis. The CHADS2 score was a useful scheme of evaluating not only stroke risk but also risk of SCI in Japanese NVAF patients.

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Renin-Angiotensin System Blockade Safely Reduces Blood Pressure in Patients With Minor Ischemic Stroke During the Acute Phase

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The ACCESS (Acute Candesartan Cilexetil Therapy in Stroke Survivors) study found that administration of candesartan in the acute phase of stroke confers a long-term benefit in patients who have sustained acute ischemic stroke. This treatment did not significantly reduce blood pressure (BP) during the acute phase, however. We assessed the short-term safety of reducing BP with renin-angiotensin system blockade in hypertensive patients who sustained acute ischemic stroke. Our randomized study compared the effects of 14 days of oral candesartan (4 mg/day), perindopril (4 mg/day), or conventional therapy (topical nitrate only when systolic BP (SBP) was ≥220 mm Hg or diastolic BP (DBP) was ≥120 mm Hg) administered to hypertensive patients within 72 hours of the onset of minor ischemic stroke. We assessed neurologic symptoms using the National Institutes of Health Stroke Scale and the modified Rankin Scale within 72 hours of stroke onset before and after drug therapy. A total of 40 patients completed the protocol. Therapy with candesartan and perindopril reduced SBP/DBP values by 23/11 mm Hg (SBP, $P < .01$; DBP, $P = .07$) and 14/0 mm Hg (SBP, $P = .07$), respectively, compared with conventional treatment. Neurologic symptoms worsened in 2 patients who received perindopril, which has no statistical significance, despite the BP reduction in patients given candesartan or perindopril. Our findings indicate that low doses of candesartan or perindopril safely reduce SBP in hypertensive patients with acute ischemic stroke. **Key Words:** Acute ischemic stroke—antihypertensive treatment—candesartan—perindopril—neurologic symptoms.

Several observational studies have shown that elevated blood pressure (BP) values immediately after stroke are associated with poor clinical outcome or mortality.[1-3] However, the current general consensus[4] is that BP should not be lowered during the acute phase unless the patient has excessive hypertension (diastolic BP [DBP] > 120 mm Hg or systolic BP [SBP] > 220 mm Hg); requires urgent antihypertensive treatment (eg, aortic dissection), or requires preparation for thrombolytic therapy. Lowering BP during the acute phase of ischemic stroke might lead to neurologic worsening by reducing regional cerebral perfusion and expanding the irreversible ischemic area in the tissues surrounding the ischemic core (the so-called "penumbra"), because cerebrovascular autoregulation is transiently impaired in this area.[5-7]

Although aggressive BP reduction during the acute phase could be detrimental to cerebral perfusion, high BP values also might increase the risk of hemorrhagic transformation of the infarction, the development of brain edema, or further hypertensive organ damage.

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Theoretically, lowering BP from the early stage of stroke might prevent early recurrent stroke or forestall further vascular events; however, several small studies of aggressive antihypertensive treatment for acute ischemic stroke have reported neutral, adverse, and favorable outcomes.[8-13] A large randomized controlled trial (the ACCESS Study)[14] has shown that the early administration of the angiotensin II type 1 receptor blocker (ARB) candesartan cilexetil in acute ischemic stroke reduces long-term (1 year) cardiovascular morbidity and mortality. Nevertheless, the safety of using candesartan to lower BP during the acute phase remains unclear, because BP values did not significantly differ between the candesartan- and placebo-treated groups in the ACCESS Study. On the other hand, angiotensin-converting enzyme (ACE) inhibitors have been found to lower BP without decreasing cerebral blood flow in patients with hypertension,[15] ischemic stroke,[16,17] and carotid stenosis or occlusion.[18]

Why the early administration of candesartan after stroke did not decrease BP during the acute phase compared with placebo in the ACCESS Study remains unclear. However, oral administration of the ACE inhibitor lisinopril initiated within 24 hours of stroke onset significantly reduced BP even at low doses.[12] Consequently, we examined whether early oral administration of low doses of the ARB candesartan or the ACE inhibitor perindopril significantly decreased BP during the acute phase of stroke. We then evaluated the short-term safety of reducing BP with these drugs using neurologic and functional measures in hypertensive patients with acute ischemic stroke.

Patients and Methods

Patient Selection

Casual brachial artery BP was measured in patients admitted to our hospital (Itabashi Chuo Medical Center) with the onset of a motor deficit due to acute ischemic stroke within 36 hours. The inclusion criteria were similar to those described for the ACCESS Study.[14] Patients with mean values of at least 2 BP measurements of ≥200 mm Hg for SBP and/or ≥110 mm Hg for DBP at 6-24 hours after stroke onset, or ≥180 and/or ≥105 mm Hg at 24-36 hours after stroke onset, were invited to participate in the study. All patients underwent baseline 12-lead electrocardiography, biochemical and hematologic measurements, chest X-ray, magnetic resonance imaging, magnetic resonance angiography (MRA), and carotid ultrasonography at admission. Exclusion criteria were intracranial hemorrhage, age >85 years, moderate to severe neurologic symptoms (National Institutes of Health Stroke Scale [NIHSS] score >8), consciousness disorders that precluded oral drug administration, any occlusions or >70% stenoses of major vessels confirmed by carotid ultrasound and intracranial MRA, and other conditions explicitly requiring BP reduction, such as malignant hypertension, manifest cardiac failure, aortic dissection, and preparation for thrombolytic therapy. Patients who had received antihypertensive or vasoactive drugs at admission also were excluded from participating in the study. Patients were categorized by stroke subtype according to the TOAST classification system.[19] Our institution's Ethics Committee approved the study design. Written informed consent to participate was obtained from all patients, who were subsequently enrolled between February 2005 and May 2007.

Drug Administration

Patients were randomized to receive one of the following regimens: 4 mg candesartan cilexetil daily, 4 mg perindopril daily, or conventional antihypertensive treatment comprising topical nitrate only when SBP was ≥220 mm Hg or DBP was ≥120 mm Hg, according to current recommendations.[4] Patients were allocated to each group in order of the date of admission. Neurologic symptoms and severity were assessed using the NIHSS and the modified Rankin Scale (mRS). Drugs were administered within 72 hours of onset of stroke symptoms immediately after baseline evaluations. The same evaluations were repeated 14 days later, and the results were compared with baseline values. The NIHSS score was checked twice each day (morning and evening) up to day 14. Drug administration was discontinued when deterioration of the NIHSS score by 1 point or more coincided with a BP reduction of ≥15%.

BP Measurement

Nurses used a semiautomatic sphygmomanometer (model ES-H51; Terumo, Tokyo, Japan) to measure BP at least every 4 hours until 2 days after the baseline values were obtained and then 3 times daily (morning, daytime, and evening) for the next 12 days. After 5 minutes of supine rest, 3 brachial BP readings were obtained, and the middle value of these was taken as casual BP if the values differed by <10 mm Hg. The BP value of the day was defined as that obtained closest to 08:00 each day except for the baseline value, which was defined as that determined immediately before drug administration to the interventional groups.

Statistical Methods

Differences in baseline factors among the 3 groups were statistically compared using single-factor analysis of variance (ANOVA) for age, time to baseline assessment from stroke onset, BP values at admission and baseline, and NIHSS score. Differences in baseline and outcome parameters between groups were assessed using the χ^2 test where appropriate. Differences in daily BP values in the 3 groups were statistically analyzed using the Student *t*-test. Changes in neurologic severity assessed by the

NIHSS and mRS between baseline and day 14 among the 3 groups were compared using single-factor ANOVA. Statistical significance was taken at the level of 5% using StatView 5.0 (SAS Institute, Cary, NC) and a personal computer running Windows.

Results

Among 372 consecutive patients who were admitted to our hospital due to acute ischemic stroke, 44 who were eligible for the present study were randomly allocated to groups and administered with candesartan (4 mg/day), perindopril (4 mg/day), or conventional therapy. Four patients were withdrawn for reasons unrelated to treatment (Fig 1). Baseline data were finally obtained from 40 patients (Table 1). All of these patients were treated with intravenous sodium ozagrel or argatroban as antithrombotic therapy during the acute phase, but the proportion of use of these drugs did not differ among the 3 groups. During the study period, no patients in either the candesartan- or perindopril-treated group reported any mediation side effects, such as dizziness or dry cough.

Figure 2 shows the time course of the BP values. The mean BP at admission in all groups was 201/109 mm Hg, and this was spontaneously reduced by 20/9 mm Hg at the time of the baseline assessment. These changes in mean BP did not differ significantly among the 3 groups. The mean duration from stroke onset to the baseline assessment was 41 hours for the conventionally treated group, 48 hours for the candesartan-treated group, and 41 hours for the perindopril-treated group (not significantly different; $P = .63$). The mean SBP and DBP values in the conventionally treated group decreased spontaneously and gradually until day 14, and only 1 patient required topical nitrate for excessive hypertension. The mean SBP in the candesartan- and perindopril-treated groups also declined until day 14 and decreased significantly at days 1, 2, 3, and 5-14 in the candesartan-treated group and at days 3 and 13 in perindopril-treated group compared with the conventionally treated group. On the other hand, the mean DBP in the candesartan-treated group decreased significantly compared with the conventionally treated group at days 2 and 13, and mean DBP in the perindopril-treated group did not differ statistically from that in the conventionally treated group during the observational period. At day 14, the changes in SBP/DBP from baseline were −21/−10 mm Hg in the conventionally treated group, −39/−26 mm Hg in the candesartan-treated group, and −35/−11 mm Hg in the perindopril-treated group. At day 14, SBP was reduced significantly (by 23 mm Hg) in the candesartan-treated group compared with the conventionally treated group ($P < .01$), whereas that in the perindopril-treated group was reduced by 14 mm Hg, but the difference did not reach statistical significance ($P = .07$). At day 14, DBP was reduced by 11 mm Hg in the candesartan-treated group compared with the conventionally treated group, but the difference did not reach statistical significance ($P = .07$), and DBP values were similar in the perindopril-treated and conventionally treated groups.

Figure 3 shows individual changes in NIHSS and mRS scores. Neurologic symptoms worsened in 2 patients in the perindopril-treated group (open circles) on days 3 and 5. These patients continued receiving daily perindopril (4 mg) after the neurologic deterioration due to persistent high BP. Neurologic symptoms remained stable in all other patients during the observational period;

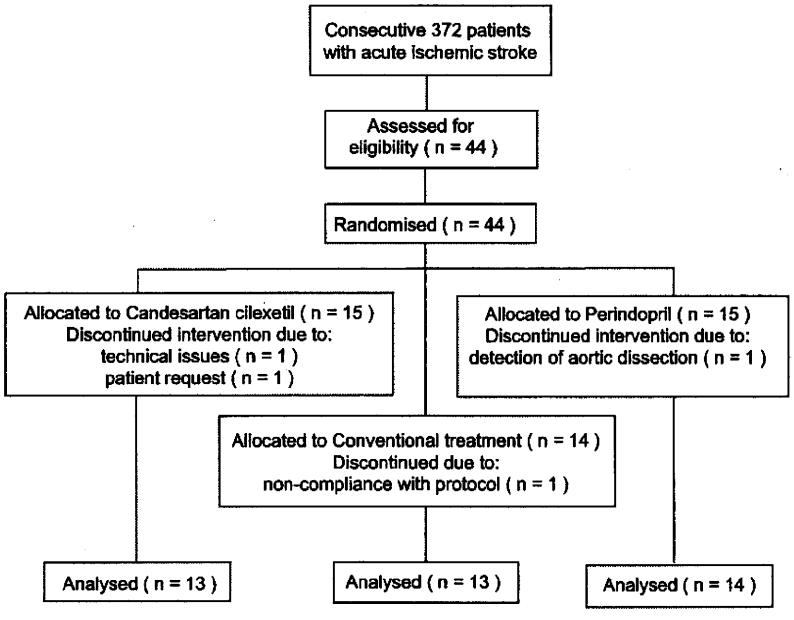

Figure 1. *Flow diagram of the patients recruited to the study.*

Table 1. *Baseline data of study participants*

Drug allocation	Conventional treatment	Candesartan cilexetil	Perindopril	*P*
Number of patients	13	13	14	
Age, years	81 ± 8	61 ± 12	62 ± 6	.02
Male gender	11	11	11	.89
TOAST classification	8 SVO, 5 UD	9 SVO, 1 CE, 3 UD	10 SVO, 4 UD	
Time to baseline from stroke onset, hours	41 ± 25	48 ± 23	41 ± 12	.63
BP at admission, mm Hg				
SBP	201 ± 12	199 ± 13	204 ± 12	.52
DBP	107 ± 20	110 ± 10	111 ± 21	.73
BP at baseline, mm Hg				
SBP	183 ± 15	178 ± 19	182 ± 16	.71
DBP	98 ± 14	104 ± 11	101 ± 10	.50
NHSS score at baseline	3.8 ± 1.8	3.6 ± 2.0	3.1 ± 1.3	.48
Medical history				
Hypertension	13 (100)	13 (100)	14 (100)	NA
Diabetes mellitus	2 (15)	3 (23)	4 (29)	.71
Hyperlipidemia	1 (8)	3 (23)	2 (14)	.54
Smoking habit	6 (46)	4 (31)	7 (50)	.57
Previous stroke or transient ischemic attack	1 (8)	0 (0)	0 (0)	NA
Atrial fibrillation	1 (8)	1 (8)	0 (0)	NA

Data are given as number of patients (%) or as mean ± standard deviation.
CE, cardioembolism; SVO, small-vessel occlusion; UD, stroke of undetermined etiology; NA, not analyzed.

however, the proportions of patients with neurologic deterioration did not differ statistically between perindopril and candesartan or conventional treatment (candesartan or conventional treatment, 0%; perindopril, 14%; χ^2 test, both $P = .48$). Between baseline and day 14, the changes in mean NIHSS score were −1.5 in the conventionally treated group, −1.5 in the candesartan-treated group, and −1.1 in the perindopril-treated group, and changes in mean mRS score were −1.0, −0.8, and −0.9, respectively. The changes in mean NIHSS and mRS scores between baseline and day 14 did not differ significantly among the 3 groups ($P = .51$ and .70, respectively).

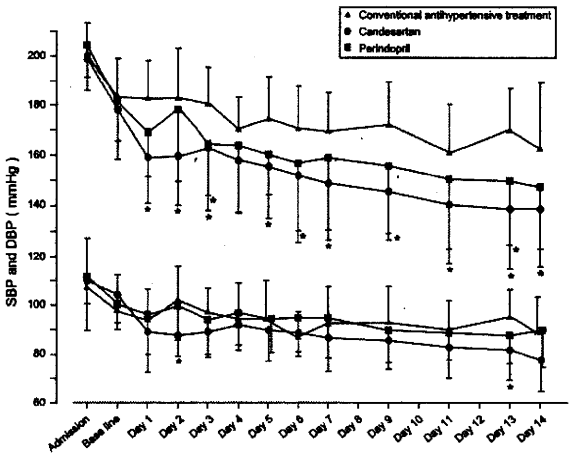

Figure 2. *Course of SBP and DBP from admission to day 14. Data are presented as mean ± standard deviation (bars). *Statistically significant BP reduction after candesartan or perindopril administration compared with conventional antihypertensive treatment for SBP and DBP (P < .05).*

Discussion

We have shown that the early administration of a low dose of candesartan cilexetil or perindopril decreased BP in hypertensive patients with acute ischemic stroke. Candesartan significantly reduced SBP compared with conventional treatment, as did perindopril, but to a lesser extent. The usual dosages of these drugs in Japan are 4-8 mg/day (maximum, 12 mg) for candesartan and 2-4 mg/day (maximum 8 mg) for perindopril. Candesartan reportedly reduces BP more effectively than ACE inhibitors at the standard dosages of either drug in patients with mild to moderate hypertension.[20] Considering this, we predicted that candesartan or perindopril at 4 mg/day would equally reduce BP. The dose of either drug might have been too low to affect highly elevated BP, but we established 4 mg/day specifically to avoid an excessive reduction. This dose of both candesartan and perindopril indeed reduced mean BP compared with conventional treatment. A previous study found that the ACE inhibitor lisinopril significantly reduces BP levels during the acute phase of ischemic stroke even at low doses.[12] Therefore, low doses of ARBs or ACE inhibitors should be a safe and effective antihypertensive treatment for patients with acute ischemic stroke.

During the study period, neurologic symptoms worsened in 2 patients in the perindopril-treated group at days 3 and 5. Both of these patients had small-vessel

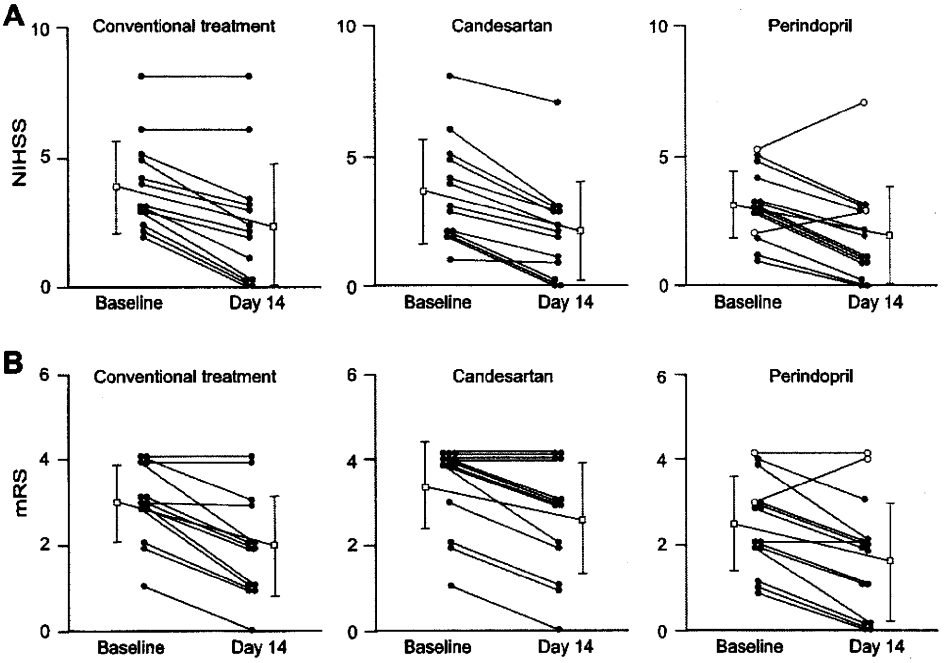

Figure 3. *Individual changes in NIHSS (A) and mRS (B) scores. Open circles (○) in the perindopril-treated group indicate patients with deteriorated NIHSS score during the observational period. Open squares (□) represent mean NIHSS or mRS score. Data are presented as mean ± standard deviation.*

occlusion (lacunar infarction), and the neurologic deterioration was not accompanied by an excessive reduction in BP. The neurologic deterioration that occasionally develops during the first few days in patients with lacunar infarction is not necessarily associated with a reduction in BP.[21] The reason why the neurologic symptoms worsened in these 2 patients is unknown, but the degree of deterioration was mild. In contrast, no patients in the candesartan-treated group exhibited worsened neurologic symptoms during the observational period despite significant BP reductions. The ACCESS Study also found no worsening of neurologic symptoms in patients given candesartan starting in the acute phase, although BP did not differ from those given placebo.[14] Although the population of the present study was too small to determine statistical differences in the proportion of patients with neurologic deterioration who received candesartan and perindopril, candesartan might have exerted some unique, BP-independent neuroprotective effects, as several experimental studies have already shown.[22-24]

Current guidelines[4] recommend antihypertensive treatment during the acute phase of stroke only for excessive hypertension or a few specific indications, although no definite evidence supports this recommendation. Several small studies have applied aggressive antihypertensive treatment from the early phase of stroke using various agents. Theoretically, calcium channel antagonists exert cerebroprotective effects by limiting postischemic intracellular calcium influx and by preferentially dilating cerebral blood vessels. The randomized Intravenous Nimodipine West European Trial (INWEST) evaluated whether the calcium channel antagonist nimodipine delivered intravenously within 24 hours of stroke is neuroprotective and improves neurologic and functional outcomes in acute stroke.[9] The results showed that unfavorable outcomes among patients treated with nimodipine were associated with decreased BP, although reanalysis of some of the data demonstrated that favorable outcomes were associated with higher BP among treated patients with mild to moderate stroke.[25] The β-blockers should limit catecholamine-induced cardiac and neurologic damage and reduce the metabolic demands of the ischemic brain. However, trials of β-blockers in monotherapy or in combination have identified a nonsignificant increase in mortality and worsened neurologic and functional outcomes after 6 months compared with a placebo, despite a significant drop in BP.[8] Although thiazide diuretics have proven benefits in the primary and secondary prevention of stroke, bendrofluazide administered within 96 hours after stroke does not decrease BP;[10] therefore, bendrofluazide is unsuitable if BP reduction is required during the immediate poststroke phase. A more recent study found that the oral ACE inhibitor lisinopril administered within 24 hours of stroke onset significantly reduced BP and did not affect neurologic and functional measures, although 1 patient developed fluctuating dysarthria and withdrew from the study.[12] Furthermore, the CHHIPS (Controlling Hypertension and Hypotension Immediately Post-Stroke) trial found that lisinopril or labetalol significantly reduced BP without increasing serious events in acute stroke.[13] The ACCESS Study confirmed the long-term benefit of early candesartan administration in acute ischemic stroke;[14]

however, the short-term safety in case of reducing BP during the acute phase was unclear, because early candesartan administration did not significantly reduce BP. Therefore, the present study provides new insight into the safety of reducing BP with candesartan during the acute phase.

In conclusion, our findings demonstrate that even a low dose of candesartan safely and significantly reduced BP in hypertensive patients with acute ischemic stroke without worsening neurologic symptoms. Perindopril also reduced BP in these patients, but to a lesser extent than candesartan. The ACCESS Study has already demonstrated that early candesartan administration confers long-term benefits via BP-independent mechanisms;[14] therefore, the early use of candesartan in acute stroke not only should be safe when the need for BP reduction is urgent, but also should protect against further vascular events. Our findings should be interpreted with caution, however, because of the small number of patients in this study. Further, larger-scale studies are needed. Several studies to assess antihypertensive therapy in acute ischemic stroke, including COSSACS (Continue Or Stop post-Stroke Antihypertensives Collaborative Study), are currently underway.

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Risk Factors for Small Cortical Infarction on Diffusion-Weighted Magnetic Resonance Imaging in Patients With Acute Ischemic Stroke

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Diffusion-weighted magnetic resonance imaging (MRI) is sensitive for detecting acute ischemic lesions. The present study evaluated risk factors associated with small cortical infarction (SCI) on diffusion-weighted MRI. We analyzed 123 patients with acute ischemic stroke retrospectively. We defined an SCI as a cortical lesions <1.5 cm in diameter detected by diffusion-weighted MRI. Risk factors and comorbidities included hypertension, hypercholesterolemia, diabetes mellitus, cigarette smoking, potential cardiac sources of embolism, carotid disease, and coagulopathy. Carotid disease was defined as >50% stenosis or occlusion in the internal carotid artery, detected by carotid ultrasonography. In addition, we analyzed plasma levels of coagulation and fibrinolysis markers. We also compared carotid disease, potential cardiac sources, and coagulopathy among localization of SCI. SCI was identified in 22.8% of patients with acute ischemic stroke. Carotid disease (odds ratio [OR] = 4.4; 95% confidence interval [CI] = 1.7-11.42; P = .002) and coagulopathy (OR = 6.8; 95% CI = 1.33-35.17; P = .02) were found to be independent risk factors for SCI. SCI with carotid disease was not associated with bilateral and multiple territorial lesions, whereas SCI with coagulopathy was associated with bilateral lesions. No borderzone lesions were found in SCI patients with cardiac sources. Our findings suggest that carotid disease and coagulopathy are independent risk factors for SCI. Localization of SCI varies depending on the underlying diseases. **Key Words:** Small cortical infarction—acute ischemic stroke—diffusion-weighted magnetic resonance imaging—carotid artery disease—coagulopathy.

The advent of diffusion-weighted magnetic resonance imaging (MRI), or DWI, greatly increased the ability to detect small cortical infarctions (SCIs). Some claim that DWI is superior to conventional T2-weighted or proton-density MRI for detecting previous minor strokes and transient ischemic attacks.[1,2] SCIs are easily confused with signals of cerebrospinal fluid on T2-weighted or proton-density MRI. Furthermore, small, disseminated satellite lesions are silent and may go unrecognized when <1 cm in diameter. The high signal-to noise ratio of DWI allows detection of disseminated small lesions on the cortical edge that might be missed on conventional T2-weighted imaging.[3] Recent studies have found that multiple small lesions visible on DWI are likely caused by emboli from a cardiac source or carotid occlusive disease.[3-5] Another study of microembolic signals (MES) detected by transcranial Doppler (TCD) found an association between MES and carotid occlusive disease and spotty lesions in the cortex.[6] These results lend support to the hypothesis that the predominant mechanism of SCI is mainly emboli from carotid disease.

Although numerous previous studies have explored carotid disease with small infarcts in the cortical area

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and multiple infarcts, including cortical small lesions, the mechanisms of SCI have received little attention. In this study, we examined vascular risk factors and blood coagulation parameters in patients with and without SCIs and compared these risk factors with localization of the lesions to investigate the etiology of SCI.

Subjects and Methods

The study group comprised 123 patients (82 men and 41 women; mean age, 67.8 years) who were consecutively admitted with acute ischemic stroke to the Tokyo Women's Medical University Hospital and underwent DWI examination between September 2003 and January 2006. The following clinical data were investigated for all patients: blood chemistry studies, coagulation testing, urinalysis, chest radiography, electrocardiography, echocardiography, MRI, magnetic resonance angiography (MRA), 24-hour electrocardiographic monitoring, and carotid ultrasonography. MRI was performed using a 1.5 T system (Toshiba Excelart, Toshiba, Japan, Philips Intera, Philips, the Netherlands, GE Signa: GE medical systems, USA, or Shemens Vision: Shemens, Germany) equipped with single-shot ecoplanar imaging. Multimodal MRI included axial T1-weighted, T2-weighted, fluid-attenuated inversion recovery, MRA, and DWI sequences. The exact sequence parameters were as follows: TR/TE, 6000/130, 3014/78, 1000/100.7, or 4000/100; matrix size, 128 × 128, 256 × 256, 128 × 128, or 96 × 128; field of view, 270 × 300, 250 × 250, 220 × 220, or 220 × 220; slice thickness, 7 mm; b-values, 1000 s/mm^2. Diffusion gradients were applied in successive scans in each of the x, y, and z directions, and a DWI image was formed from the average of these values. SCI was defined as a cortical hyperintense lesion with diameter of <1.5 cm on DWI.

Differences in gender, age, risk factors for stroke, and plasma levels of coagulation markers between patients with SCI and without SCI were analyzed. The risk factors included hypertension (blood pressure >140/90 mm Hg or a history of hypertension requiring medical treatment), hypercholesterolemia (serum total cholesterol level >220 mg/dL or a history of hypercholesterolemia requiring medical treatment), diabetes mellitus (glycosylated hemoglobin level >6.5% or a history of treatment with an oral glucose depressant or insulin), regular cigarette smoking, and potential cardiac sources of embolism, including atrial fibrillation, patent foramen ovale, and thrombus in the left atrium. Duplex ultrasound and power Doppler ultrasound (Toshiba SSA-350A and SSA-550A) were used to detect carotid artery stenosis or occlusion.[7] European Carotid Surgery Trial (ECST) criteria were used to define carotid stenosis. To exclude carotid occlusion due to cardiac embolism in cardiac disease, cases with both carotid occlusion and potential cardiac sources were classified only as potential cardiac sources, not carotid disease. We also investigated a history of Trousseau's syndrome (ie, coagulopathy induced by cancer) and antiphospholipid syndrome (fulfilling the Sapporo criteria[8]), both of which were classified as coagulopathy. Coagulation markers included β-thromboglobulin (βTG), platelet factor 4 (PF4), thrombin-antithrombin III complex (TAT), and D-dimer. βTG and PF4 were measured using Asserachrom βTG kit and PF4 kits (Diagnostica Stago, Asnèires, France), TAT was measured using the TAT SRL kit (SRL, Tokyo, Japan), and D-dimer was measured using the Lpia-ace D-dimer kit (Mitsubishi Kagaku Iatron, Tokyo, Japan). Plasma levels of these hemostatic markers were quantified by enzyme-linked immunosorbent assay.

The localization of SCIs was classified as bilateral lesions, territorial single circulation (anterior or posterior circulation) lesions, territorial multiple circulation (bilateral or anterior and posterior circulation) lesions, or borderzone lesions (Fig 1). Borderzone lesions were defined as SCIs in superficial borderzone areas. Six of 7 SCI patients with bilateral lesions were categorized as having territorial multiple circulation lesions. One SCI patient with bilateral lesions who had a coagulopathy as a risk factor had lesions in bilateral borderzones, and was categorized as having borderzone lesions. Risk factors, including carotid disease, coagulopathy, and potential cardiac sources, were compared among the various SCI localization categories.

Statistical Analysis

All data were entered into SPSS version 7.5 for Windows (SPSS, Chicago, IL) for analysis. Differences in the prevalence of risk factors among patients with and without SCI were analyzed using the χ^2 test for the variables with 5 or more possible values. Fisher's exact test was used to analyze the prevalence of the lesion patterns of SCI for the nominal variables with fewer than 5 possible values. The Mann-Whitney U test was used to test the distribution of the continuous variables, such as age and plasma level of coagulation markers, between patients with and without SCI. These risk factors also were analyzed as independent determinants for SCI by multiple logistic regression analysis. The results are expressed as odds ratio (OR) of relative risk, with 95% confidence interval (CI). Statistical significance was established as $P < .05$.

Results

SCI was detected in 28 of 123 patients (22.8%). Carotid disease was significantly associated with SCI (Table 1), and all of the patients with SCI had the lesions on the same side with carotid disease. There were no significant differences in age, gender, or the prevalence of diabetes mellitus, hypertension, hypercholesterolemia, cigarette smoking, or potential cardiac sources between patients with and without SCI. Multiple logistic regression analysis

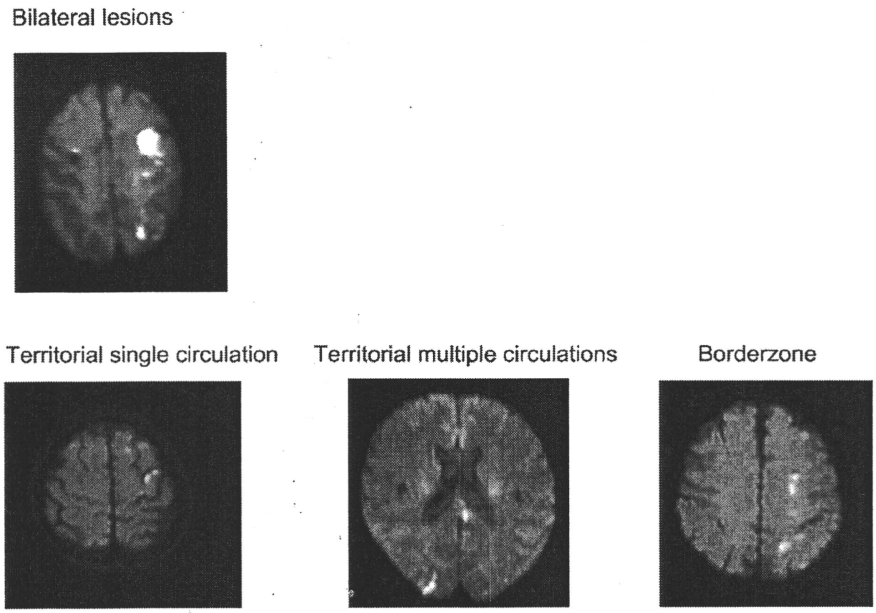

Figure 1. *We classified the localizations of SCI into bilateral lesions, territorial single circulation (anterior or posterior circulation), territorial multiple circulation (bilateral or anterior and posterior circulations), and borderzone lesions. Borderzone lesions were defined as SCI in superficial borderzone areas.*

found that carotid disease (OR = 3.9; 95% CI = 1.5-10.0; P = .004) and coagulopathy (OR = 6.7; 95% CI = 1.33-35.17; P = .02) were independent risk factors for SCI (Table 2). Analysis of plasma levels of coagulation parameters revealed no significant differences between patients with and without SCI (Table 3). Likewise, there were no significant differences in plasma levels of coagulation parameters between SCI patients with carotid disease and those with coagulopathy (data not shown).

Table 4 summarizes the localization of SCI and underlying diseases. Among the SCI patients, 13 had carotid disease, 8 had potential cardiac sources, 4 had coagulopathy, and 6 had unidentified sources of infarctions. Risk factors overlapped in 3 patients displaying the following pathology: carotid disease and potential cardiac sources, carotid disease and coagulopathy, and potential cardiac sources and coagulopathy. Bilateral lesions were less closely associated with carotid disease (P = .009); on the other hand, SCI with coagulopathy was associated with bilateral lesions (P = .038). Territorial multiple circulation lesions were less closely associated with carotid disease (P = .037) and more closely associated with coagulopathy (P = .058). No borderzone lesions were found in any SCI patient with potential cardiac sources.

Table 1. *Background characteristics of patients with and without small cortical infarcts (SCIs)*

Characteristic	SCI (+) (n = 28)	SCI (−) (n = 95)	P value*
Age, years, ± SD	69.8 ± 14.1	67.0 ± 13.4	.21†
Male gender (%)	21 (75.0%)	61 (64.2%)	.36
Diabetes mellitus	15 (53.6%)	42 (44.2%)	.40
Hypertension	18 (64.2%)	65 (68.4%)	.65
Hypercholesterolemia	12 (42.9%)	39 (41.1%)	1.00
Cigarette smoking	12 (42.9%)	44 (46.3%)	.55
Potential cardiac sources	8 (28.6%)	20 (21.1%)	.46
Atrial fibrillation	6	19	
Patent foramen ovale	1	1	
Thrombus in left atrium	1	0	
Carotid disease	13 (46.4%)	12 (12.6%)	.001
Occlusion	3	3	
Mean degree of stenosis	75.2 ± 21.4	70.0 ± 21.7	.56†
Coagulopathy	4 (14.3%)	5 (5.3%)	.21
Trousseau's syndrome	3	2	
Antiphospholipid syndrome	1	3	

*χ^2 test unless indicated otherwise.
†Mann-Whitney U test.