49 Bui AL, Katz R, Kestenbaum B, et al. Cystatin C and carotid intima-media thickness in asymptomatic adults: the Multi-Ethnic Study of Atherosclerosis (MESA). *Am J Kidney Dis* 2009; **53:** 389–98.

50 Zhang L, Zhao F, Yang Y, et al. Association between carotid artery intima-media thickness and early-stage CKD in a Chinese population. *Am J Kidney Dis* 2007; **49:** 786–92.

51 Ishizaka N, Ishizaka Y, Toda E, et al. Association between chronic kidney disease and carotid intima-media thickening in individuals with hypertension and impaired glucose metabolism. *Hypertens Res* 2007; **30:** 1035–41.

52 Lemos MM, Jancikic AD, Sanches FM, et al. Intima-media thickness is associated with inflammation and traditional cardiovascular risk factors in non-dialysis-dependent patients with chronic kidney disease. *Nephron Clin Pract* 2010; **115:** c189–94.

53 Zoungas S, Ristevski S, Lightfoot P, et al. Carotid artery intima-medial thickness is increased in chronic renal failure. *Clin Exp Pharmacol Physiol* 2000; **27:** 639–41.

54 Briet M, Bozec E, Laurent S, et al. Arterial stiffness and enlargement in mild-to-moderate chronic kidney disease. *Kidney Int* 2006; **69:** 350–57.

55 Preston E, Ellis MR, Kulinskaya E, Davies AH, Brown EA. Association between carotid artery intima-media thickness and cardiovascular risk factors in CKD. *Am J Kidney Dis* 2005; **46:** 856–62.

56 Zhou W, Ni Z, Yu Z, Shi B, Wang Q. Brain natriuretic peptide is related to carotid plaques and predicts atherosclerosis in pre-dialysis patients with chronic kidney disease. *Eur J Intern Med* 2012; **23:** 539–44.

57 Kokubo Y. Carotid atherosclerosis in kidney disease. *Contrib Nephrol* 2013; **179:** 35–41.

58 Kokubo Y, Nakamura S, Okamura T, et al. Relationship between blood pressure category and incidence of stroke and myocardial infarction in an urban Japanese population with and without chronic kidney disease: the Suita Study. *Stroke* 2009; **40:** 2674–79.

59 Ohara T, Kokubo Y, Toyoda K, et al. Impact of chronic kidney disease on carotid atherosclerosis according to blood pressure category: the Suita study. *Stroke* 2013; **44:** 3537–39.

60 Mancia G, De Backer G, Dominiczak A, et al, and the Management of Arterial Hypertension of the European Society of Hypertension, and the European Society of Cardiology. 2007 Guidelines for the Management of Arterial Hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens* 2007; **25:** 1105–87.

61 Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 2013; **9:** 63–75.

62 Koushik NS, McArthur SF, Baird AD. Adult chronic kidney disease: neurocognition in chronic renal failure. *Neuropsychol Rev* 2010; **20:** 33–51.

63 Etgen T, Chonchol M, Förstl H, Sander D. Chronic kidney disease and cognitive impairment: a systematic review and meta-analysis. *Am J Nephrol* 2012; **35:** 474–82.

64 Elias MF, Dore GA, Davey A. Kidney disease and cognitive function. *Contrib Nephrol* 2013; **179:** 42–57.

65 Kurella Tamura M, Wadley V, Yaffe K, et al. Kidney function and cognitive impairment in US adults: the Reasons for Geographic and Racial Differences in Stroke (REGARDS) Study. *Am J Kidney Dis* 2008; **52:** 227–34.

66 Kurella M, Yaffe K, Shlipak MG, Wenger NK, Chertow GM. Chronic kidney disease and cognitive impairment in menopausal women. *Am J Kidney Dis* 2005; **45:** 66–76.

67 Hailpern SM, Melamed ML, Cohen HW, Hostetter TH. Moderate chronic kidney disease and cognitive function in adults 20 to 59 years of age: Third National Health and Nutrition Examination Survey (NHANES III). *J Am Soc Nephrol* 2007; **18:** 2205–13.

68 Jassal SV, Roscoe J, LeBlanc D, Devins GM, Rourke S. Differential impairment of psychomotor efficiency and processing speed in patients with chronic kidney disease. *Int Urol Nephrol* 2008; **40:** 849–54.

69 Elias MF, Elias PK, Seliger SL, Narsipur SS, Dore GA, Robbins MA. Chronic kidney disease, creatinine and cognitive functioning. *Nephrol Dial Transplant* 2009; **24:** 2446–52.

70 Davey A, Elias MF, Robbins MA, Seliger SL, Dore GA. Decline in renal functioning is associated with longitudinal decline in global cognitive functioning, abstract reasoning and verbal memory. *Nephrol Dial Transplant* 2013; **28:** 1810–19.

71 Helmer C, Stengel B, Metzger M, et al. Chronic kidney disease, cognitive decline, and incident dementia: the 3C Study. *Neurology* 2011; **77:** 2043–51.

72 Murray AM, Knopman DS. Cognitive impairment in CKD: no longer an occult burden. *Am J Kidney Dis* 2010; **56:** 615–18.

73 Radić J, Ljutić D, Radić M, Kovačić V, Sain M, Curković KD. The possible impact of dialysis modality on cognitive function in chronic dialysis patients. *Neth J Med* 2010; **68:** 153–57.

74 Kuwashiro T, Sugimori H, Ago T, Kamouchi M, Kitazono T, and the FSR Investigators. Risk factors predisposing to stroke recurrence within one year of non-cardioembolic stroke onset: the Fukuoka Stroke Registry. *Cerebrovasc Dis* 2012; **33:** 141–49.

75 Słowik A, Turaj W, Iskra T, Strojny J, Szczudlik A. Microalbuminuria in nondiabetic patients with acute ischemic stroke: prevalence, clinical correlates, and prognostic significance. *Cerebrovasc Dis* 2002; **14:** 15–21.

76 Tsagalis G, Akrivos T, Alevizaki M, et al. Renal dysfunction in acute stroke: an independent predictor of long-term all combined vascular events and overall mortality. *Nephrol Dial Transplant* 2009; **24:** 194–200.

77 Cuadrado-Godia E, Ois A, Garcia-Ramallo E, et al. Biomarkers to predict clinical progression in small vessel disease strokes: prognostic role of albuminuria and oxidized LDL cholesterol. *Atherosclerosis* 2011; **219:** 368–72.

78 Yokota C, Minematsu K, Ito A, Toyoda K, Nagasawa H, Yamaguchi T. Albuminuria, but not metabolic syndrome, is a significant predictor of stroke recurrence in ischemic stroke. *J Neurol Sci* 2009; **277:** 50–53.

79 Luo Y, Wang X, Wang Y, et al, and the CNSR Investigators. Association of glomerular filtration rate with outcomes of acute stroke in type 2 diabetic patients: results from the china national stroke registry. *Diabetes Care* 2014; **37:** 173–79.

80 Ng DP, Fukushima M, Tai BC, et al. Reduced GFR and albuminuria in Chinese type 2 diabetes mellitus patients are both independently associated with activation of the TNF-alpha system. *Diabetologia* 2008; **51:** 2318–24.

81 McCarthy ET, Sharma R, Sharma M, et al. TNF-alpha increases albumin permeability of isolated rat glomeruli through the generation of superoxide. *J Am Soc Nephrol* 1998; **9:** 433–38.

82 Rodríguez-Yáñez M, Castellanos M, Blanco M, et al. Micro- and macroalbuminuria predict hemorrhagic transformation in acute ischemic stroke. *Neurology* 2006; **67:** 1172–77.

83 Beamer NB, Coull BM, Clark WM, Wynn M. Microalbuminuria in ischemic stroke. *Arch Neurol* 1999; **56:** 699–702.

84 Toyoda K, Okada Y, Jinnouchi J, et al. High blood pressure in acute ischemic stroke and underlying disorders. *Cerebrovasc Dis* 2006; **22:** 355–61.

85 Covic A, Schiller A, Mardare NG, et al. The impact of acute kidney injury on short-term survival in an Eastern European population with stroke. *Nephrol Dial Transplant* 2008; **23:** 2228–34.

86 Tsagalis G, Akrivos T, Alevizaki M, et al. Long-term prognosis of acute kidney injury after first acute stroke. *Clin J Am Soc Nephrol* 2009; **4:** 616–22.

87 Hao Z, Wu B, Lin S, et al. Association between renal function and clinical outcome in patients with acute stroke. *Eur Neurol* 2010; **63:** 237–42.

88 Ovbiagele B, Pineda S, Saver JL. Renal dysfunction and discharge destination in patients with intracerebral hemorrhage. *J Stroke Cerebrovasc Dis* 2011; **20:** 145–49.

89 Cutting S, Castro C, Lee VH, Prabhakaran S. Impaired renal function is not associated with increased volume of intracerebral hemorrhage. *J Stroke Cerebrovasc Dis* 2014; **23:** 86–90.

90 Koga M, Toyoda K, Yamagami H, et al, and the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement Study Investigators. Systolic blood pressure lowering to 160 mmHg or less using nicardipine in acute intracerebral hemorrhage: a prospective, multicenter, observational study (the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement-Intracerebral Hemorrhage study). *J Hypertens* 2012; **30:** 2357–64.

91 Sato S, Koga M, Yamagami H, et al. Conjugate eye deviation in acute intracerebral hemorrhage: Stroke Acute Management with Urgent Risk-factor Assessment and Improvement–ICH (SAMURAI-ICH) study. *Stroke* 2012; **43:** 2898–903.

92 Sakamoto Y, Koga M, Yamagami H, et al, and the SAMURAI Study Investigators. Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement–Intracerebral Hemorrhage study. *Stroke* 2013; **44:** 1846–51.

93 Qureshi AI, Palesch YY, Martin R, et al. Systolic blood pressure reduction and risk of acute renal injury in patients with intracerebral hemorrhage. *Am J Med* 2012; **125:** 718.

94 Jardine MJ, Ninomiya T, Perkovic V, et al. Aspirin is beneficial in hypertensive patients with chronic kidney disease: a post-hoc subgroup analysis of a randomized controlled trial. *J Am Coll Cardiol* 2010; **56:** 956–65.

95 Olesen JB, Lip GY, Kamper AL, et al. Stroke and bleeding in atrial fibrillation with chronic kidney disease. *N Engl J Med* 2012; **367:** 625–35.

96 Angiolillo DJ, Bernardo E, Capodanno D, et al. Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. *J Am Coll Cardiol* 2010; **55:** 1139–46.

97 Lai HM, Aronow WS, Kalen P, et al. Incidence of thromboembolic stroke and of major bleeding in patients with atrial fibrillation and chronic kidney disease treated with and without warfarin. *Int J Nephrol Renovasc Dis* 2009; **2:** 33–37.

98 Yang F, Chou D, Schweitzer P, Hanon S. Warfarin in haemodialysis patients with atrial fibrillation: what benefit? *Europace* 2010; **12:** 1666–72.

99 Chan KE, Lazarus JM, Thadhani R, Hakim RM. Anticoagulant and antiplatelet usage associates with mortality among hemodialysis patients. *J Am Soc Nephrol* 2009; **20:** 872–81.

100 Hirano T. Thrombolysis and hyperacute reperfusion therapy for stroke in renal patients. *Contrib Nephrol* 2013; **179:** 110–18.

101 Hishida A. Clinical analysis of 207 patients who developed renal disorders during or after treatment with edaravone reported during post-marketing surveillance. *Clin Exp Nephrol* 2007; **11:** 292–96.

102 Protack CD, Bakken AM, Saad WE, Davies MG. Influence of chronic renal insufficiency on outcomes following carotid revascularization. *Arch Surg* 2011; **146:** 1135–41.

103 Sidawy AN, Aidinian G, Johnson ON 3rd, White PW, DeZee KJ, Henderson WG. Effect of chronic renal insufficiency on outcomes of carotid endarterectomy. *J Vasc Surg* 2008; **48:** 1423–30.

104 van Lammeren GW, Moll FL, Blankestijn PJ, et al. Decreased kidney function: an unrecognized and often untreated risk factor for secondary cardiovascular events after carotid surgery. *Stroke* 2011; **42:** 307–12.

105 Kamouchi M, Kumagai N, Okada Y, Origasa H, Yamaguchi T, Kitazono T. Risk score for predicting recurrence in patients with ischemic stroke: the Fukuoka stroke risk score for Japanese. *Cerebrovasc Dis* 2012; **34:** 351–57.

106 Lip GY, Andreotti F, Fauchier L, et al, and the European Heart Rhythm Association. Bleeding risk assessment and management in atrial fibrillation patients. Executive Summary of a Position Document from the European Heart Rhythm Association [EHRA], endorsed by the European Society of Cardiology [ESC] Working Group on Thrombosis. *Thromb Haemost* 2011; **106:** 997–1011.

107 Martin U, Sponer G, Strein K. Influence of hepatic and renal failure on pharmacokinetic properties of the novel recombinant plasminogen activator BM 06.022 in rats. *Drug Metab Dispos* 1993; **21:** 236–41.

108 Lyrer PA, Fluri F, Gisler D, Papa S, Hatz F, Engelter ST. Renal function and outcome among stroke patients treated with IV thrombolysis. *Neurology* 2008; **71:** 1548–50.

109 Agrawal V, Rai B, Fellows J, McCullough PA. In-hospital outcomes with thrombolytic therapy in patients with renal dysfunction presenting with acute ischaemic stroke. *Nephrol Dial Transplant* 2010; **25:** 1150–57.

110 Aronow WS. Acute and chronic management of atrial fibrillation in patients with late-stage CKD. *Am J Kidney Dis* 2009; **53:** 701–10.

111 Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J* 2006; **151:** 713–19.

112 Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010; **138:** 1093–100.

113 James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014; **311:** 507–20.

114 Merkin SS, Diez Roux AV, Coresh J, Fried LF, Jackson SA, Powe NR. Individual and neighborhood socioeconomic status and progressive chronic kidney disease in an elderly population: The Cardiovascular Health Study. *Soc Sci Med* 2007; **65:** 809–21.

115 Toyoda K, Fujii K, Fujimi S, et al. Stroke in patients on maintenance hemodialysis: a 22-year single-center study. *Am J Kidney Dis* 2005; **45:** 1058–66.

116 Toyoda K, Fujii K, Ando T, Kumai Y, Ibayashi S, Iida M. Incidence, etiology, and outcome of stroke in patients on continuous ambulatory peritoneal dialysis. *Cerebrovasc Dis* 2004; **17:** 98–105.

117 Seliger SL, Gillen DL, Longstreth WT Jr, Kestenbaum B, Stehman-Breen CO. Elevated risk of stroke among patients with end-stage renal disease. *Kidney Int* 2003; **64:** 603–09.

118 van der Sande FM, Hermans MM, Leunissen KM, Kooman JP. Noncardiac consequences of hypertension in hemodialysis patients. *Semin Dial* 2004; **17:** 304–06.

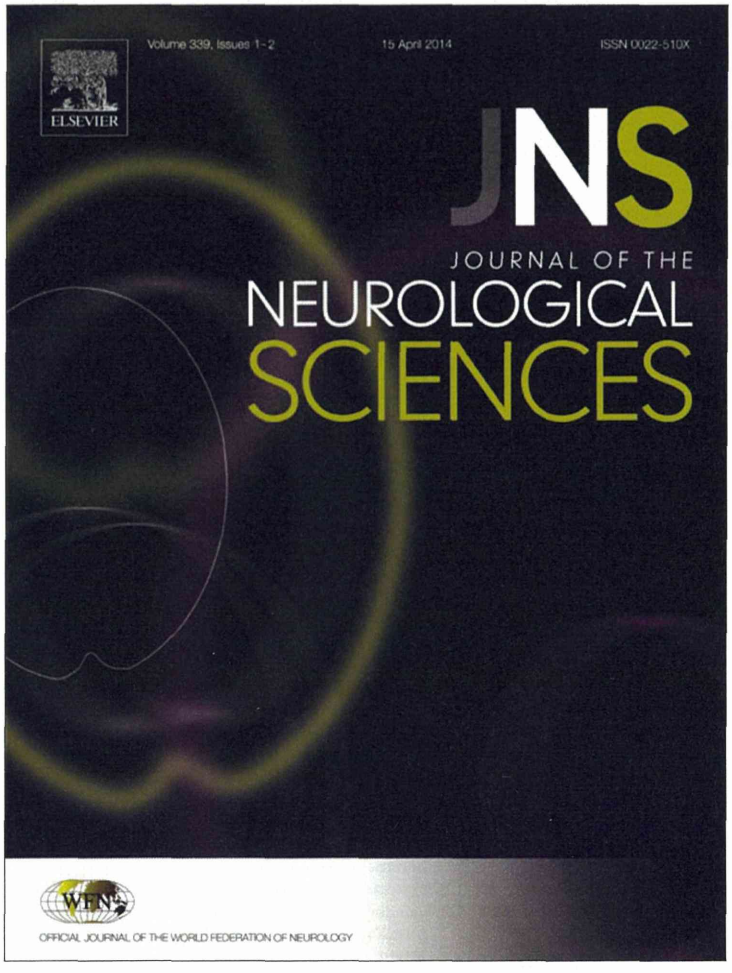
119 Imai E, Matsuo S, Makino H, et al. Chronic Kidney Disease Japan Cohort study: baseline characteristics and factors associated with causative diseases and renal function. *Clin Exp Nephrol* 2010; **14:** 558–70.

120 Toyoda K, Kumai Y, Fujii K, Ando T, Ibayashi S. Simultaneous onset of haemorrhagic and ischaemic strokes in a haemodialysis patient. *J Neurol Neurosurg Psychiatry* 2002; **72:** 673–74.

121 Iseki K. Stroke feature and management in dialysis patients. *Contrib Nephrol* 2013; **179:** 100–09.

122 Naganuma M, Mori M, Nezu T, et al, and the SAMURAI Study Investigators. Intravenous recombinant tissue plasminogen activator therapy for stroke patients receiving maintenance hemodialysis: the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA registry. *Eur Neurol* 2011; **66:** 37–41.

123 Palacio S, Gonzales NR, Sangha NS, Birnbaum LA, Hart RG. Thrombolysis for acute stroke in hemodialysis: international survey of expert opinion. *Clin J Am Soc Nephrol* 2011; **6:** 1089–93.



Journal of the Neurological Sciences 339 (2014) 113–117

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Etiological mechanisms of isolated pontine infarcts based on arterial territory involvement

Junpei Kobayashi [a], Tomoyuki Ohara [a,*], Kazuo Minematsu [a], Kazuyuki Nagatsuka [b], Kazunori Toyoda [a]

[a] Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan
[b] Department of Neurology, National Cerebral and Cardiovascular Center, Suita, Japan

ARTICLE INFO

Article history:
Received 7 December 2013
Received in revised form 9 January 2014
Accepted 29 January 2014
Available online 6 February 2014

Keywords:
Basilar artery
Brain stem
Cardioembolism
Diffusion-weighted imaging
Risk factors
Stroke

ABSTRACT

Background: Pontine infarcts can be classified into four regions based on the vascular anatomy: anteromedial, anterolateral, lateral and posterior. The purpose of this study was to determine if different etiological mechanisms are responsible for these four types of pontine infarcts.
Methods: We studied consecutive patients within 7 days of symptom onset who had isolated pontine infarcts on diffusion-weighted imaging. The factors associated with infarct topography were determined by multivariate logistic regression analysis.
Results: A total of 205 patients were enrolled (78 women; mean age, 72 ± 11 years). The distribution of the infarcts was anteromedial in 73%, anterolateral in 14%, lateral in 3% and posterior in 10%. In multivariate logistic regression analysis, major cardioembolic sources (odds ratio (OR), 4.17; 95% confidence interval (CI), 1.21–14.1) and previous ischemic stroke (OR, 2.92; 95% CI, 1.09–7.89) were positively associated with lateral or posterior infarcts compared with anteromedial infarcts. In contrast, advanced age (OR, 0.55; 95% CI, 0.35–0.81 per 10-year increase), diabetes mellitus (OR, 0.31; 95% CI, 0.11–0.80) and basilar artery disease (OR, 0.27; 95% CI, 0.08–0.75) were negatively associated with lateral or posterior pontine infarcts.
Conclusions: Baseline characteristics were significantly different among patients with isolated pontine infarcts in different topographic locations. Our results suggest that cardioembolism is relatively common in lateral or posterior pontine infarcts, whereas basilar artery atherosclerosis is more common in anteromedial infarcts.

1. Introduction

The clinico-topographic correlation of isolated pontine infarcts has been investigated [1–7]. However, the etiological mechanisms of isolated pontine infarcts based on arterial perfusion territories remain unclear. According to arterial anatomy, pontine perfusion territories can be categorized into four groups: anteromedial, anterolateral, lateral and posterior [8]. The anteromedial and anterolateral territories are supplied by basilar arterial branches; the lateral territory is supplied by long circumferential branches from the basilar artery, the anterior inferior cerebellar artery (AICA) and the superior cerebellar artery (SCA); and the posterior territory is supplied by only by the SCA [8,9]. Therefore, it is possible that there are some differences in underlying etiology of pontine stroke depending upon the artery involved.

There have been only a few studies on underlying mechanisms of isolated pontine infarcts based on arterial involvement [3,5]. Furthermore, all pontine infarcts in these previous studies were not identified by diffusion-weighted imaging (DWI). DWI seems superior to conventional imaging in selecting patients with acute isolated pontine infarcts because it can distinguish fresh infarcts from old ones and can accurately exclude concomitant extrapontine acute ischemic lesions such as small cortical infarcts.

The purposes of this study were to determine if stroke etiology in isolated pontine infarcts diagnosed by MRI including DWI depends upon the artery involved and to determine the clinical features in each pontine infarct.

2. Methods

2.1. Patient selection and evaluation

From a database of patients admitted to our department between January 2006 and June 2012, we retrospectively identified patients with an isolated pontine infarct within 7 days of symptom onset who underwent MRI and magnetic resonance angiography (MRA). The diagnosis of the isolated pontine infarct was based on DWI findings. Stroke subtypes were principally categorized by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [10]. Electrocardiography, 24-hour electrocardiographic monitoring, and carotid ultrasound were performed on the first day of admission in all patients. Transthoracic echocardiogram was performed as a cardiac evaluation for most patients, while transesophageal echocardiogram was performed depending on

* Corresponding author at: Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan. Tel.: +81 6 6833 5012; fax: +81 6 6835 5267.
E-mail address: ohatomo@ncvc.go.jp (T. Ohara).

0022-510X/$ – see front matter © 2014 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jns.2014.01.039

the decision of attending neurologists. The hospital's ethics committee approved this study, which was based on a retrospective review of our stroke database.

2.2. MRI methods and analysis

MRI, including DWI and MRA, was performed at 1.5 T (Magnetom Vision; Siemens Medical Solutions, Erlangen, Germany). DWI was performed using the following parameters: repetition time, 4000 ms; echo time, 100 ms; matrix, 128 × 128; field of view, 23 cm; section thickness, 4 mm; intersection gap, 2 mm; and b values, 0 and 1000 s/mm^2. MRA was obtained using the following parameters: repetition time, 35 ms; echo time, 7.6 ms; flip angle, 20°; field of view, 200 mm; matrix, 224 × 512; and slice thickness, 0.6 mm.

Pontine lesions were estimated by two board-certified neurologists (J.K. and T.O.). The pontine infarcts were classified into four groups (anteromedial, anterolateral, lateral and posterior) according to the brain map of the arterial perfusion territories (Fig. 1) [8]. When the judgment of the two neurologists was inconsistent, a decision was made by discussion. Representative cases of isolated pontine infarcts are shown in Fig. 2.

Based on the results of basilar artery assessment, patients were categorized into three groups (normal, wall irregularity, >50% stenoocclusive lesion) [11]. Basilar artery disease was defined as the latter two pathologies at the level of pontine infarct. Old lacunar infarcts were defined as cavitated lesions (3–15 mm) in the territory of the deep perforating arteries on FLAIR imaging. White matter lesions were defined as a large confluent area in the deep white matter corresponding to grade 3 of the Fazekas criteria [12].

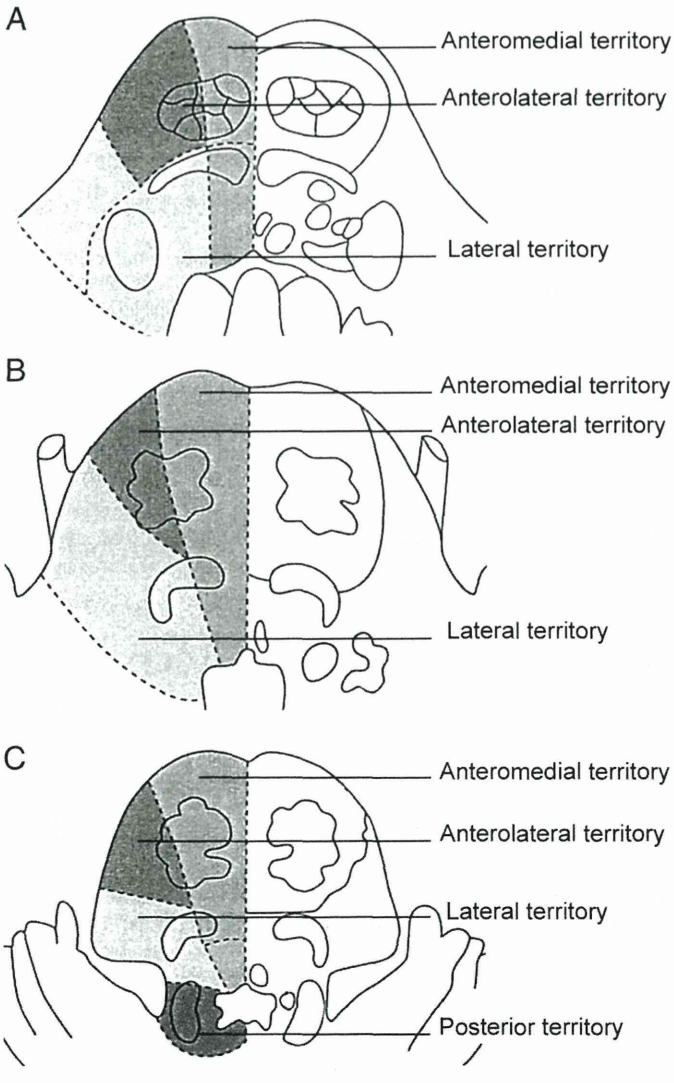


Fig. 1. Vascular perfusion territories of the pons (modified from Tatu L. et al. [8]). A: Lower pons. B: Middle pons. C: Upper pons.

2.3. Clinical characteristics

The patients' clinical characteristics, including sex, age and cardiovascular risk factors including diabetes mellitus, hypertension, dyslipidemia, smoking and alcohol consumption, were recorded. In addition, major cardioembolic sources of stroke including atrial fibrillation (AF), a previous history of ischemic stroke, coronary artery disease and peripheral artery disease were identified. Major cardioembolic sources were defined by high risk of cardioembolism in TOAST criteria [10]. AF was diagnosed based on either ECG recordings or a confirmed history of AF. Clinical findings, including hemiparesis, sensory disturbance and oculomotor disturbance, were also collected. The National Institutes of Health Stroke Scale (NIHSS) on admission and the modified Rankin Scale (mRS) scores at hospital discharge (median hospital stay, 18 days) were evaluated. A favorable outcome was defined as mRS scores of 0 to 1, and an unfavorable outcome as mRS scores of 2 to 6.

2.4. Statistical analysis

Differences in clinical features among the four groups were analyzed using the Kruskal–Wallis test for continuous values and Fisher's exact test for categorical variables. To identify variables in baseline characteristics and radiological findings associated with infarct topography, simple logistic regression analyses were performed. The lateral and posterior pontine infarcts were grouped together as a lateral-posterior (LP) group for the purpose of regression analysis, because both of these areas are mainly supplied by cerebellar arteries. The anterolateral and LP groups were compared with the anteromedial group serving as a reference. Multivariate logistic regression analyses were performed to determine the independent factors associated with infarct topography using all of the demographic, clinical and radiographic variables. A backward selection procedure was performed using $P > 0.10$ for the likelihood ratio test for exclusion of variables. A P value <0.05 was considered statistically significant. All statistical analyses were conducted using PASW for windows version 17.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 3099 patients with acute ischemic stroke were admitted to our hospital during the study period. Among them, 231 (7.5%) consecutive patients had acute pontine infarcts (181 [78%] were admitted within 48 h of symptom onset). Finally, a total of 205 patients (78 women; mean age, 72 ± 11 years) with acute isolated pontine infarcts were enrolled in this study, excluding patients with contraindication for MRI by implanted cardiac devices (n = 9), pontine infarcts involving multiple vascular territories (n = 16), or lack of intracranial MRA study (n = 1). Of all isolated pontine infarcts, 149 (73%) belonged to the anteromedial group, 28 (14%) to the anterolateral group, 7 (3%) to the lateral group and 21 (10%) to the posterior group.

Clinical presentations are shown in Table 1. Pure motor hemiparesis ($P < 0.001$), sensory disturbance ($P = 0.004$), oculomotor disturbance ($P < 0.001$) and initial NIHSS score ($P < 0.001$) were significantly different among these four categories. Pure motor hemiparesis (PMH) was common in patients with an anteromedial pontine infarct, and sensory and oculomotor disturbances were common in patients with a lateral infarct. There were significant differences among the four groups in functional outcome at hospital discharge ($P < 0.001$). Patients with an anteromedial pontine infarct had a higher rate (67%) of unfavorable outcome (Fig. 3).

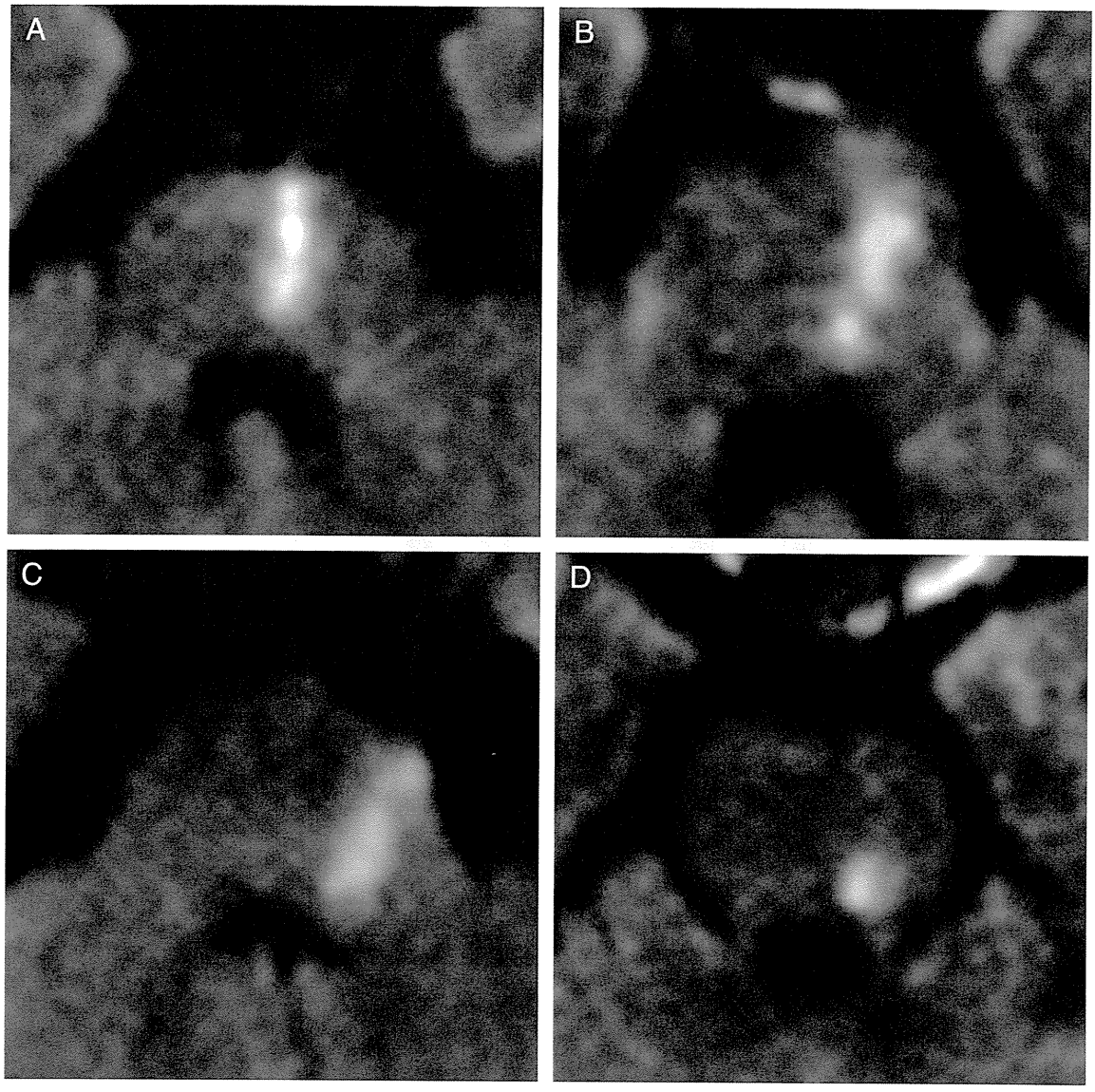


Fig. 2. Pontine infarct locations based on DWI. A: anteromedial pontine infarct. B: anterolateral pontine infarct. C: lateral pontine infarct. D: posterior pontine infarct.

Baseline characteristics and radiological findings of the patients are shown in Table 2. In univariate analyses, there were no significant differences between the anteromedial and anterolateral groups. In the LP group, age (OR, 0.63; 95%CI, 0.42–0.91) was younger and diabetes mellitus (OR 0.38; 95%CI, 0.15–0.94) and basilar artery disease (OR 0.36; 95%CI, 0.14–0.95) were less frequent than in the anteromedial group. Multivariate logistic regression analysis demonstrated that basilar artery disease (OR 0.39; 95%CI, 0.14–0.96) and female sex (OR 0.37; 95%CI, 0.14–0.93) were negatively associated with anterolateral infarcts compared with anteromedial infarcts (Table 3, Model A). Compared with anteromedial infarcts, Major cardioembolic sources (mainly AF) (OR 4.17; 95%CI, 1.21–14.1) and previous ischemic stroke (OR 2.92; 95%CI, 1.09–7.89) were positively associated with LP infarcts, whereas age (OR 0.55; 95%CI, 0.35–0.81), diabetes mellitus (OR 0.31; 95%CI, 0.11–0.80) and basilar artery disease (OR 0.27; 95%CI, 0.08–0.75) were negatively associated with LP infarcts (Table 3, Model B).

Table 1
Clinical features based on the location of pontine infarcts.

	AM (N = 149)	AL (N = 28)	Lat (N = 7)	Post (N = 21)	P value
Clinical presentation					
Pure motor hemiparesis, n (%)	82 (55%)	14 (50%)	2 (29%)	1 (5%)	<0.001
Sensorimotor stroke, n (%)	41 (27%)	3 (11%)	0 (0%)	5 (24%)	0.114
Sensory disturbance, n (%)	48 (32%)	11 (39%)	4 (57%)	15 (71%)	0.004
Oculomotor disturbance, n (%)	7 (5%)	3 (11%)	2 (29%)	6 (29%)	<0.001
Initial NIHSS score, median (IQR)	4 (2.5–5)	3 (1–5.8)	2 (0–3)	2 (1–3)	<0.001
Functional outcome					
Unfavorable outcome, n (%)	100 (67%)	12 (43%)	2 (29%)	6 (29%)	<0.001

AM indicates anteromedial; AL, anterolateral; Lat, lateral; Post, posterior.

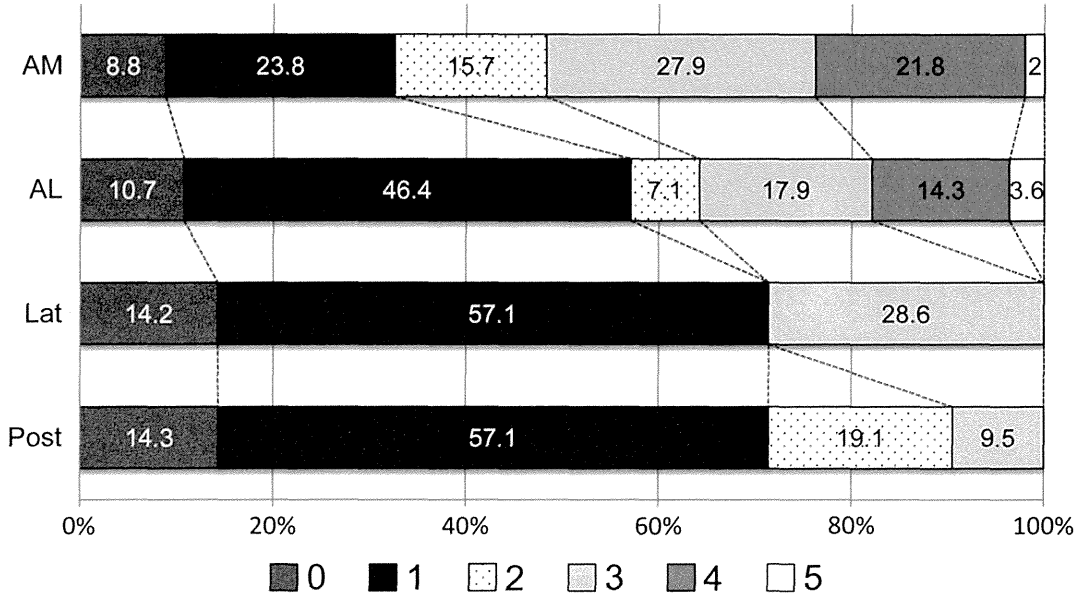


Fig. 3. Modified Rankin Scale score at hospital discharge in patients with isolated pontine infarcts at the four different locations.

4. Discussion

This is the first study to explore the underlying mechanisms of the location of isolated pontine infarcts based on assessment by MRI including DWI. The major finding of this study was that major cardioembolic sources (mainly AF) were relatively common in patients with LP pontine infarcts, whereas basilar artery atherosclerosis was relatively common in patients with anteromedial pontine infarcts.

The etiological mechanisms of isolated pontine infarcts based on arterial perfusion territories were not thoroughly assessed. Most previous studies on the etiology of pontine infarcts focused on anteromedial and anterolateral infarcts [13–18]. On the basis of pathological findings, the etiology of anteromedial pontine infarcts reaching to the basal surface of the pons is the so called basilar artery branch disease, caused by the atheromatous plaque protruding into the orifice of basilar artery branches [18], whereas small deep pontine infarcts are usually due to lipohyalinosis of perforating small arteries [17]. In contrast, previous studies on AICA or SCA territory infarcts mainly included extrapontine lesions [19-23], and etiologies of isolated pontine infarcts in the lateral or posterior territories perfused mainly by AICA and SCA were not determined.

LP infarcts occurred in 14% of our patients with isolated pontine infarcts, and major cardioembolic sources were more common in these patients than in patients with anteromedial infarcts. These results suggest that LP pontine infarcts are likely to be caused by an embolic etiology. Because the lateral and posterior pontine regions are perfused mainly by long circumferential branches such as the AICA or SCA, they may be more susceptible to embolism. On the other hand, anteromedial pontine infarcts were independently associated with basilar artery disease compared with anterolateral and LP infarcts. In addition, patients with anteromedial pontine infarcts were significantly older and more

Table 2
Baseline characteristics and radiological findings based on the location of pontine infarcts.

	AM (N = 149)	AL (N = 28)	Crude OR[a] (95%CI)	LP [Lat, Post][b] (N = 28)	Crude OR[c] (95%CI)
Women, n (%)	64 (43%)	7 (25%)	0.44 (0.17–1.11)	7 [1, 6] (25%)	0.45 (0.18–1.11)
Age, average (SD), years[d]	73 (11)	71 (12)	0.86 (0.61–1.24)	67 [66, 67] (10)	0.63 (0.42–0.91)
Risk factor					
Diabetes mellitus, n (%)	70 (47%)	14 (50%)	1.13 (0.50–2.53)	7 [3,4] (25%)	0.38 (0.15–0.94)
Hypertension, n (%)	128 (86%)	22 (79%)	0.60 (0.22–1.66)	22 [5, 17] (79%)	0.60 (0.22–1.66)
Hyperlipidemia, n (%)	93 (62%)	15 (54%)	0.69 (0.31–1.57)	15 [4, 11] (54%)	0.69 (0.31–1.57)
Major cardioembolic sources, n (%)	16 (11%)	4 (14%)	1.39 (0.42–4.50)	6 [2, 4] (21%)	2.27 (0.80–6.42)
Atrial fibrillation, n (%)	14 (9%)	4 (14%)	1.61 (0.49–5.30)	5 [2, 3] (18%)	2.10 (0.69–6.38)
Past history					
Ischemic stroke, n (%)	38 (26%)	11 (39%)	1.89 (0.81–4.39)	10 [3, 7] (36%)	1.62 (0.69–3.82)
Coronary artery disease, n (%)	23 (15%)	4 (14%)	0.91 (0.29–2.88)	1 [1, 0] (4%)	0.20 (0.03–1.57)
Peripheral artery disease, n (%)	8 (5%)	2 (7%)	1.36 (0.27–6.75)	0 [0, 0] (0%)	0.74 (0.17–5.07)
Current smoking, n (%)	41 (28%)	8 (29%)	1.05 (0.43–2.58)	12 [4,8] (43%)	1.98 (0.86–4.53)
Habitual alcohol use, n (%)	40 (27%)	8 (29%)	1.09 (0.44–2.67)	11 [3, 8] (39%)	1.76 (0.76–4.09)
Radiological findings					
Old lacunar infarcts, n (%)	62 (41%)	13 (46%)	1.22 (0.54–2.74)	11 [4, 7] (39%)	0.91 (0.40–2.07)
White matter lesions, n (%)	47 (32%)	12 (43%)	1.63 (0.71–3.71)	7 [2, 5] (25%)	0.72 (0.29–1.82)
Basilar artery disease, n (%)	64 (43%)	7 (25%)	0.44 (0.18–1.11)	6 [1, 5] (21%)	0.36 (0.14–0.95)
Steno-occlusive lesion, n (%)	19 (13%)	0 (0%)		3 [1, 2] (11%)	
Wall irregularity, n (%)	45 (30%)	7 (25%)		3 [0, 3] (11%)	

AM indicates anteromedial; AL, anterolateral; Lat, lateral; Post, posterior; LP, lateral plus posterior; OR, odds ratio; CI, confidential interval; SD, standard deviation.

[a] OR in AL compared with AM.

[b] Average or number of cases was put in bracket; the former corresponding to lateral group, the latter to posterior group.

[c] OR in LP compared with AM.

[d] OR of ages was estimated for a change of 10 years in the age variable.

Table 3
Multivariate logistic regression analysis of independent relative factors associated with infarct locations.

Model A (AL vs AM) [a]	OR	95% CI	*P Value*
Women	0.37	0.14-0.93	0.034
White matter lesions	2.25	0.23-5.46	0.074
Basilar artery disease	0.39	0.14-0.96	0.040
Model B (LP vs AM)[b]	**OR**	**95% CI**	***P Value***
Age (per 10-year increase)	0.55	0.35-0.81	0.002
Diabetes mellitus	0.31	0.11-0.80	0.015
Major cardioembolic sources	4.17	1.21-14.1	0.024
Previous ischemic stroke	2.92	1.09-7.89	0.033
Basilar artery disease	0.27	0.08-0.75	0.011

AM indicates anteromedial; AL, anterolateral; Lat, lateral; Post, posterior; LP, lateral plus posterior; OR, odds ratio; CI, confidential interval.
Multivariate analyses were performed adjusting for baseline characteristics and radiological findings selected by a backward selection procedure.
[a] Model A: AL compared with AM (as a reference).
[b] Model B: LP compared with AM (as a reference).

frequently diabetic than those with LP infarcts. These findings suggest that anteromedial infarcts were mainly caused by atherosclerotic lesions in the basilar artery such as basilar artery branch disease, and this is consistent with previous studies [13,16,18].

Our study has several methodological strengths compared with previous studies. First, we examined the association between infarct topography and etiology of stroke by classiCorrected proof. tfying pontine infarcts into four groups according to arterial perfusion territories [8]. In a few previous studies that investigated stroke etiology, the topographical classification of pontine infarcts included a group described as tegmental pontine infarcts [3,5]. However, this classification may be inappropriate because the tegmental group includes both anteromedial and posterior infarcts. Second, electrocardiography and 24-hour electrocardiographic monitoring were performed in all patients, and this may have contributed to a higher incidence of AF in our study (11%) than in previous studies [9]. Therefore, we may have performed a more accurate analysis of the association between AF and isolated pontine infarct.

This study has some limitations. First, the single-center retrospective study design might have caused selection bias and statistical errors. Second, complicated aortic arch plaque could have served as a source of emboli that caused some posterior infarcts, and it was not fully investigated. Extensive evaluation by transesophageal echocardiography may lead to better elucidation of stroke mechanisms in isolated pontine infarcts.

In conclusion, we demonstrated that major cardioembolic sources were relatively common in LP pontine infarcts and basilar artery atherosclerosis was relatively common in anteromedial infarcts. The results of our study suggest that the topographic location of isolated pontine infarcts based on arterial perfusion territories provides useful information on the etiological mechanisms. Especially in LP pontine infarcts, the sources of embolism including AF should be examined for appropriate management.

Sources of funding

This study was supported by an Intramural Research Fund (H24-6-1) for Cardiovascular Diseases of National Cerebral and Cardiovascular Center (to T.O.) and a Grant-in-Aid (H23-Junkanki-Ippan-010, Chief Investigator: Kazunori Toyoda, M.D.) from the Ministry of Health, Labour and Welfare of Japan.

Disclosure of conflict of interest

None.

Author contribution statement

1. Junpei Kobayashi: study concept and design, acquisition of data, and analysis and interpretation
2. Tomoyuki Ohara: study concept and design, critical revision on the manuscript for important intellectual content
3. Kazuo Minematsu and Kazuyuki Nagatsuka: study supervision
4. Kazunori Toyoda: critical revision on the manuscript for important intellectual content and study supervision

Acknowledgements

We thank Akiko Kada, MPH, for advice on the statistical analyses.

References

[1] Kim JS, Lee JH, Im JH, Lee MC. Syndromes of pontine base infarction. A clinical–radiological correlation study. Stroke 1995;26:950–5.
[2] Kataoka S, Hori A, Shirakawa T, Hirose G. Paramedian pontine infarction. Neurological/topographical correlation. Stroke 1997;28:809–15.
[3] Bassetti C, Bogousslavsky J, Barth A, Regli F. Isolated infarcts of the pons. Neurology 1996;46:165–75.
[4] Kataoka S, Miaki M, Saiki M, Yamaya Y, Hori A, Hirose G. Rostral lateral pontine infarction: neurological/topographical correlations. Neurology 2003;61:114–7.
[5] Kumral E, Bayulkem G, Evyapan D. Clinical spectrum of pontine infarction. Clinical-MRI correlations. J Neurol 2002;249:1659–70.
[6] Oh S, Bang OY, Chung CS, Lee KH, Chang WH, Kim GM. Topographic location of acute pontine infarction is associated with the development of progressive motor deficits. Stroke 2012;43:708–13.
[7] Toyoda K, Saku Y, Ibayashi S, Sadoshima S, Ogasawara T, Fujishima M. Pontine infarction extending to the basal surface. Stroke 1994;25:2171–8.
[8] Tatu L, Moulin T, Vuillier F, Bogousslavsky J. Arterial territories of the human brain. In: Paciaroni M, Agnelli G, Caso V, Bogousslavsky J, editors. Manifestations of Stroke, Front Neurol NeurosciBasel: Karger; 2012. p. 99–110.
[9] Field TS, Benavente OR. Penetrating artery territory pontine infarction. Rev Neurol Dis 2011;8:30–8.
[10] Adams Jr HP, Bendixen BH, Kappelle, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35–41.
[11] Uehara T, Mori E, Tabuchi M, Ohsumi Y, Yamadori A. Detection of occlusive lesions in intracranial arteries by three-dimensional time-of-flight magnetic resonance angiography. Cerebrovasc Dis 1994;4:365–70.
[12] Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 t in Alzheimer's dementia and normal aging. AJNR 1987;149:351–6.
[13] Erro ME, Gallego J, Herrera M, Bermejo B. Isolated pontine infarcts: etiopathogenic mechanisms. Eur J Neurol 2005;12:984–8.
[14] Kunz S, Griese H, Busse O. Etiology and long-term prognosis of unilateral paramedian pontine infarction with progressive symptoms. Eur Neurol 2003;50:136–40.
[15] Vemmos KN, Spengos K, Tsivgoulis G, Manios E, Zis V, Vassilopoulos D. Aetiopathogenesis and long-term outcome of isolated pontine infarcts. J Neurol 2005;252:212–7.
[16] Yamamoto Y, Ohara T, Hamanaka M, Hosomi A, Tamura A, Akiguchi I. Characteristics of intracranial branch atheromatous disease and its association with progressive motor deficits. J Neurol Sci 2011;304:78–82.
[17] Fisher CM. Lacunar strokes and infarcts: a review. Neurology 1982;32:871–6.
[18] Fisher CM, Caplan LR. Basilar artery branch occlusion: a cause of pontine infarction. Neurology 1971;21:900–5.
[19] Caplan LR, Wityk RJ, Glass TA, Tapia J, Pazdera L, Chang HM, et al. New England Medical Center Posterior Circulation registry. Ann Neurol 2004;56:389–98.
[20] Roquer J, Lorenzo JL, Pou A. The anterior inferior cerebellar artery infarcts: a clinical-magnetic resonance imaging study. Acta Neurol Scand 1998;97:225–30.
[21] Kumral E, Kisabay A, Atac C. Lesion patterns and etiology of ischemia in superior cerebellar artery territory infarcts. Cerebrovasc Dis 2005;19:283–90.
[22] Kumral E, Kisabay A, Atac C. Lesion patterns and etiology of ischemia in the anterior inferior cerebellar artery territory involvement: a clinical-diffusion weighted-MRI study. Eur J Neurol 2006;13:395–401.
[23] Takamatsu K, Ohta T. A study of infarction in the region of the anterior inferior cerebellar artery. Rinsho Shinkeigaku 1995;35:621–5.

PLOS | ONE

RESEARCH ARTICLE

Anticoagulation Intensity of Rivaroxaban for Stroke Patients at a Special Low Dosage in Japan

Takuya Okata[1], Kazunori Toyoda[1]*, Akira Okamoto[2], Toshiyuki Miyata[3], Kazuyuki Nagatsuka[4], Kazuo Minematsu[1]

1. Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, Japan, **2.** Department of Clinical Chemistory, National Cerebral and Cardiovascular Center, Osaka, Japan, **3.** Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center, Osaka, Japan, **4.** Department of Neurology, National Cerebral and Cardiovascular Center, Osaka, Japan

*toyoda@ncvc.go.jp

OPEN ACCESS

Citation: Okata T, Toyoda K, Okamoto A, Miyata T, Nagatsuka K, et al. (2014) Anticoagulation Intensity of Rivaroxaban for Stroke Patients at a Special Low Dosage in Japan. PLoS ONE 9(11): e113641. doi:10.1371/journal.pone.0113641

Editor: Giuseppe Pignataro, Federico II University of Naples, Italy

Received: June 20, 2014

Accepted: October 27, 2014

Published: November 26, 2014

Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper.

Funding: The present study was supported by Intramural Research Funds (23-4-3, 25-6-4) for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: KT, TM, KN, and KM report speakers' honoraria from Bayer. Kazunori Toyoda and Toshiyuki Miyata are PLOS ONE Editorial Board members. This, in addition to the previously declared competing interests, does not alter the authors' adherence to PLOS ONE Editorial policies and criteria.

Abstract

Objectives: In Japan, low-dose rivaroxaban [15 mg QD/10 mg QD for creatinine clearance of 30–49 mL/min] was approved for clinical use in NVAF patients partly because of its unique pharmacokinetics in Japanese subjects. The aim of the study was to determine the anticoagulation intensity of rivaroxaban and its determinant factors in Japanese stroke patients.

Methods: Consecutive stroke patients with NVAF admitted between July 2012 and December 2013 were studied. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and estimated plasma concentration of rivaroxaban (C_{riv}) based on an anti-factor Xa chromogenic assay were measured just before and 4 and 9 h after administration at the steady state level of rivaroxaban. Determinant factors for C_{riv} were explored using a linear mixed-model approach.

Results: Of 110 patients (37 women, 75±9 years old), 59 took 15 mg QD of rivaroxaban and 51 took 10 mg QD. C_{riv} at 4 h was 186 ng/mL for patients taking 15 mg QD and 147 ng/mL for those taking 10 mg QD. Both PT and aPTT were positively correlated with C_{riv}. C_{riv} was 72% lower at 4 h in 15 patients receiving crushed tablets than in the other patients, and tablet crushing was significantly associated with lower C_{riv} (adjusted estimate −0.43, 95% CI −0.60 to −0.26) after multivariate-adjustment.

Conclusion: The anticoagulation effects of rivaroxaban in the acute stroke setting for Japanese NVAF patients were relatively low as compared with those in the ROCKET-AF and J-ROCKET AF trials. Tablet crushing, common in dysphagic patients, decreased C_{riv}.

Introduction

Atrial fibrillation (AF) is associated with an increased risk of stroke and thromboembolism, and effective antithrombotic therapy significantly reduces this risk [1]. Oral anticoagulant therapy with vitamin K antagonists (VKAs) has been established as the standard for stroke prevention in patients with AF [2]. Recently, novel oral anticoagulants (NOACs) have emerged as an alternative to VKAs for thromboembolic prevention in patients with nonvalvular AF (NVAF). Among these, rivaroxaban (Bayer Schering Pharma AG, Wuppertal, Germany) is an oral direct activated coagulation factor X (FXa) inhibitor that binds directly to the catalytic site of the serine protease FXa independently of antithrombin and inhibits both free and prothrombinase-bound FXa [3].

To reduce the risk of stroke and systemic embolism in patients with NVAF, special low dosages of rivaroxaban are recommended in Japan; i.e. 15 mg quaque die (QD) for patients with creatinine clearance (CrCl) $\geq$50 mL/min, and 10 mg QD for those with CrCl of 15–49 mL/min, as compared to globally approved dosages of 20 mg QD and 15 mg QD, respectively. This recommendation was based on the unique pharmacokinetics in Japanese subjects showing higher rivaroxaban exposure than Caucasian subjects when using the same dosage [4], and the Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (J-ROCKET AF) proved the safety and efficacy of this low-dose rivaroxaban medication in Japanese NVAF patients [5]. However, the anticoagulation effect of rivaroxaban, especially with the low dosage, has been understudied in the acute stroke setting because acute stroke patients were excluded in the above pharmacokinetics study and trial. For example, the ROCKET-AF, J-ROCKET AF, RELY, and ENGAGE AF-TIMI 48 excluded acute stroke patients within 14 days after onset [5, 6, 7, 8], and the ARISTOTLE excluded those within 7 days from enrollment [9]. Thus, these major trials did not prove the efficacy and safety of NOACs for acute stroke patients at all. Various clinical conditions associated with stroke, such as highly advanced age, differences in drug administration, and potential damage to the kidney and other organs by acute stroke effects, might affect anticoagulation intensity. To examine the issue of the anticoagulation effect of rivaroxaban in clinical practice, the aim was to determine the anticoagulation intensity of rivaroxaban and its determinant factors in Japanese patients with stroke.

Methods

Ethic Statement

The study conformed to the guiding principles of the Declaration of Helsinki and was approved by the local ethics committee of National Cerebral and Cardiovascular Center. All patients or their next of kin gave their written informed consent to participate.

Patients and demographic data

Among patients admitted to our cerebrovascular unit due to stroke and transient ischemic attack (TIA) from July 2012 through December 2013 (recruitment interrupted from August 2013 to November 2013 due to technical problems), data of patients who had NVAF and started to take rivaroxaban for the prevention of stroke and systemic embolism were collected prospectively.

The baseline characteristics of patients, including components of the $CHADS_2$ and CHA_2DS_2-VASc scores, weight, National Institutes of Health Stroke Scale (NIHSS) score, renal function, and other medications on the day of blood collection, as well as whether the rivaroxaban tablet was crushed, were recorded. Renal function was expressed as CrCl using the Cockcroft and Gault equation.

Blood Collection and Measurements of Coagulation Assays

All patients took rivaroxaban after breakfast. Blood sampling was performed at least 2 days after rivaroxaban was started, when its concentration was considered to have reached steady state. Two venous blood samples were collected each time in citrate-containing tubes just before (0 h) and 4 h and 9 h after drug administration. The sampling point at 4 h was meant to capture the maximum concentration of rivaroxaban because the maximum concentration has been reported to occur 1 to 3 h after tablet intake and to be delayed by 2 h with food [10]. The sampling point at 9 h was meant to reflect the half-life of rivaroxaban, which has been reported to be 11 to 13 h in the elderly, partly due to renal dysfunction [11]. For 1 of the 2 tubes, following double centrifugation at 2,500 g for 15 min, platelet-poor plasma was collected, quick-frozen, and stored at −80℃ until the analysis for anti-FXa activity was performed. Blood samples were drawn into a citrate-containing tube using a 21-gauge needle. The prothrombin time (PT, Recombiplastin [Instrumentation Laboratory, Bedford, MA, USA] and activated partial thromboplastin time (aPTT, Actin [Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA]) were measured immediately, and the calibrated plasma rivaroxaban concentration (C_{riv}) was analyzed based on the anti-FXa activity (anti-factor Xa chromogenic assay, STA-Liquid Anti-Xa [Diagnostica Stago, Asnières, France]) of the stored samples. Anti-factor Xa chromogenic assays have previously been shown to have acceptable accuracy and precision [12], and they have been recommended for quantitative measurements of rivaroxaban exposure, using rivaroxaban calibrators with results expressed as ng/mL of rivaroxaban. The minimum detectable sensitivity of estimated rivaroxaban concentration based on the anti-factor Xa chromogenic assay was 10 ng/mL. If the estimated rivaroxaban concentration was below the limit of detection, it was treated as 5 ng/mL for convenience. These assays were all measured on a STA-R coagulometer (Diagnostica Stago, Asnières, France).

Statistical analysis

Data are presented as values and percentages, means ± SD, or medians (interquartile range). Rivaroxaban concentrations were log-transformed due to right skewness of the original distributions (log C_{riv}). The baseline characteristics and laboratory profiles were compared by rivaroxaban dosage subgroup using the Wilcoxon signed-rank test for continuous variables and the chi-square test or Fisher's exact test for categorical variables.

In order to identify variables affecting rivaroxaban concentrations at the three fixed time points, a linear mixed-effects (LME) model approach was adopted. LME models are statistical models that are used in the analysis of clustered or longitudinal data. LME models estimate the relationship between the dependent variable and the predictors included in the model, accounting for both the fixed effects and the random effects of the independent variables. Compared with linear regression models without considering clustering or temporal effects, LME models are able to more accurately estimate the fixed effects by estimating the covariance structure through the inclusion of individual-specific random effects [13]. First, for the purpose of selecting the variables to be included in the model, the effects of various baseline characteristics on rivaroxaban concentrations were evaluated, using a LME model with fixed effects for each variable and time points of blood sampling and a random effect for patients. Second, variables with $P<0.20$ and time points of blood sampling were included as fixed effects in the LME model performed with rivaroxaban concentrations, whereas patients were treated as a random effect. The level of significance was set at 95% ($P=0.05$). Statistical analysis was performed using JMP, version 10.0.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patients' Characteristics

A total of 126 patients started to take rivaroxaban. Of these, seven patients who did not consent to participate, one with off-label dosage (7.5 mg QD), and eight who took rivaroxaban with the evening meal were excluded. Thus, 110 patients (37 women, 75±9 years old) were studied. All patients had breakfast or tube feeding in the morning on the day of blood collection. Fifty-nine patients (54%) took 15 mg QD of rivaroxaban, and the other 51 took 10 mg QD. Thirty-seven patients (34%) taking 10 mg QD had renal function of CrCl 30–49 mL/min. In addition, six patients with prior intracerebral hemorrhage, one with prior muscular hemorrhage, and seven very elderly patients took 10 mg QD based on the judgment of the physician in charge even though their CrCl values were 50 mL/min or greater. Eighty-four patients (76%) were hospitalized due to acute ischemic stroke, and rivaroxaban was initiated at a median of 5 days after symptom onset. Eight patients were hospitalized due to acute TIA (initiation of rivaroxaban at a median of 2.5 days), and seven were hospitalized due to acute intracerebral hemorrhage (at a median of 11 days). The other 11 patients were

Table 1. Baseline clinical characteristics of patients.

	Overall (n=110)	15 mg QD (n=59)	10 mg QD (n=51)	P value
Women	37(34)	13(22)	24(47)	0.008
Age, y	74.6±9.4	68.8±7.4	81.4±6.6	<0.001
Congestive heart failure	13(12)	3(5)	10(20)	0.035
Hypertension	70(64)	36(61)	34(67)	0.558
Diabetes mellitus	29(26)	15(25)	14(27)	0.831
Index cerebrovascular events				0.949
Acute ischemic stroke	84(76)	46(78)	38(74)	
Acute TIA	8(7)	5(9)	3(6)	
Acute intracerebral hemorrhage	7(6)	2(3)	5(10)	
Chronic ischemic stroke	11(10)	6(10)	5(10)	
Prior vascular disease	11(10)	5(9)	6(12)	0.752
$CHADS_2$	2(1–3)	1(1–2)	2(2–3)	0.001
CHA_2DS_2-VASc	3(2–4)	2(1–4)	4(3–5)	0.001
Weight	59.1±11.0	64.0±9.4	53.4±10.0	<0.001
NIHSS score on admission	4(2–14)	4(2–13)	5(1–15)	0.727
Concomitant use of antiplatelet agent	8(7)	4(7)	4(8)	0.831
Creatinine clearance (mL/min)	61.6±20.0	74.0±16.7	47.2±12.4	<0.001
30–49 mL/min	37(34)	0(0)	37(73)	<0.001
Liver dysfunction				
Child-Pugh grade B or C	0(0)	0(0)	0(0)	0.999
Tablet crushing	15(14)	5(9)	10(20)	0.103
Time from initiation of rivaroxaban to blood sampling, day	6(5–7)	6(5–7)	6(5–8)	0.625
Time from stroke/TIA onset to blood sampling, day*	12(8–15)(n=99)	12(8–13)(n=53)	12(9–15)(n=46)	0.212

Data are numbers (%), means±SD, or medians (interquartile range). *Patients with chronic ischemic stroke are excluded. TIA, transient ischemic attack; NIHSS, National Institutes of Health Stroke Scale.

doi:10.1371/journal.pone.0113641.t001

hospitalized due to chronic ischemic stroke. The baseline characteristics of the patients are shown in Table 1. Fifteen patients received crushed rivaroxaban tablets due to dysphagia (five orally and ten via a nasogastric (NG) tube of which tip placement in the stomach was confirmed by chest X-ray).

Coagulation markers and estimated rivaroxaban concentration

The distribution of plasma coagulation markers is shown in Table 2. Among the three sampling points, 99 patients (90%) reached the highest estimated concentration of rivaroxaban at 4 h, while the other 11 (10%) reached it at 9 h. The baseline characteristics of these 11 patients did not differ from those of the remaining 99 patients.

Coagulation markers and C_{riv} at 0 h, 4 h, and 9 h after administration of two different dosages are shown in Figure 1. Between the two dosage groups, there were no significant differences in aPTT and PT at all sampling points. The 15 mg QD group demonstrated higher rivaroxaban concentrations at 0 h and 9 h than

Table 2. Coagulation markers and estimated rivaroxaban concentration.

	0 h	4 h	9 h
aPTT, sec	32(29–34)	43(37–48)	37(34–41)
PT, sec	12.8(12.1–13.7)	19.4(16.7–22.3)	16.3(14.5–18.2)
PT-INR	1.04(0.98–1.11)	1.56(1.34–1.80)	1.32(1.17–1.47)
Rivaroxaban concentration, ng/mL	11(5–22)	168(109–243)	65(44–103)

aPTT, activated partial thromboplastin time; PT, prothrombin time; INR, international normalized ratio.

doi:10.1371/journal.pone.0113641.t002

the 10 mg QD group [Figure 1], and the median C_{riv} was 27% higher at 4 h (186 ng/mL vs. 147 ng/mL) and 24% higher at 9 h (73 ng/mL vs. 59 ng/mL).

Both PT and aPTT values were prolonged in a concentration-dependent manner, and they showed positive correlations with C_{riv} at 0 h, 4 h, and 9 h (Figure 2). The linearity of the relationship seen between PT and C_{riv} had a higher R^2 value than that between aPTT and C_{riv}.

In comparison to the 95 patients receiving regular tablets, the other 15 patients receiving crushed tablets showed lower rivaroxaban concentrations at all three time points [Figure 3]; the median C_{riv} was 72% lower at 4 h (54 ng/mL vs. 193 ng/mL, $P<0.001$) and 70% lower at 9 h (21 ng/mL vs. 71 ng/mL, $P<0.001$). C_{riv} did not differ between the ten patients receiving crushed tablets via an NG tube (median 46 ng/mL at 4 h) and the five patients receiving oral administration (median 69 ng/mL, $P=0.624$). After exclusion of these 15 patients, the median C_{riv} at 4 h of the 95 patients receiving regular tablets was 193 ng/mL (206 ng/mL for 54 patients on 15 mg QD and 168 ng/mL for 41 patients on 10 mg QD). The median PT (15.8 sec vs. 20.0 sec at 4 h, $P<0.001$) and aPTT values (14.5 sec vs. 16.7 sec t 4 h, $P<0.001$) were also shorter in patients receiving crushed tablets than in the other patients.

In addition to tablet crushing ($P<0.001$), congestive heart failure ($P=0.073$), diabetes mellitus ($P=0.005$), NIHSS score on admission ($P=0.022$), rivaroxaban

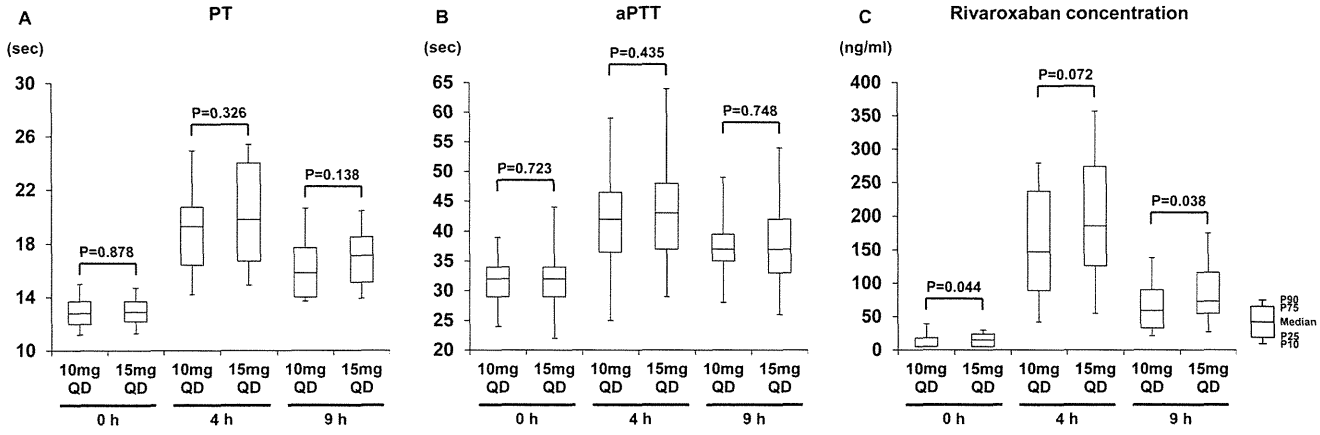


Figure 1. PT (A), aPTT (B), and rivaroxaban concentration (C_{riv}) at 0 h, 4 h, and 9 h after administration.

doi:10.1371/journal.pone.0113641.g001

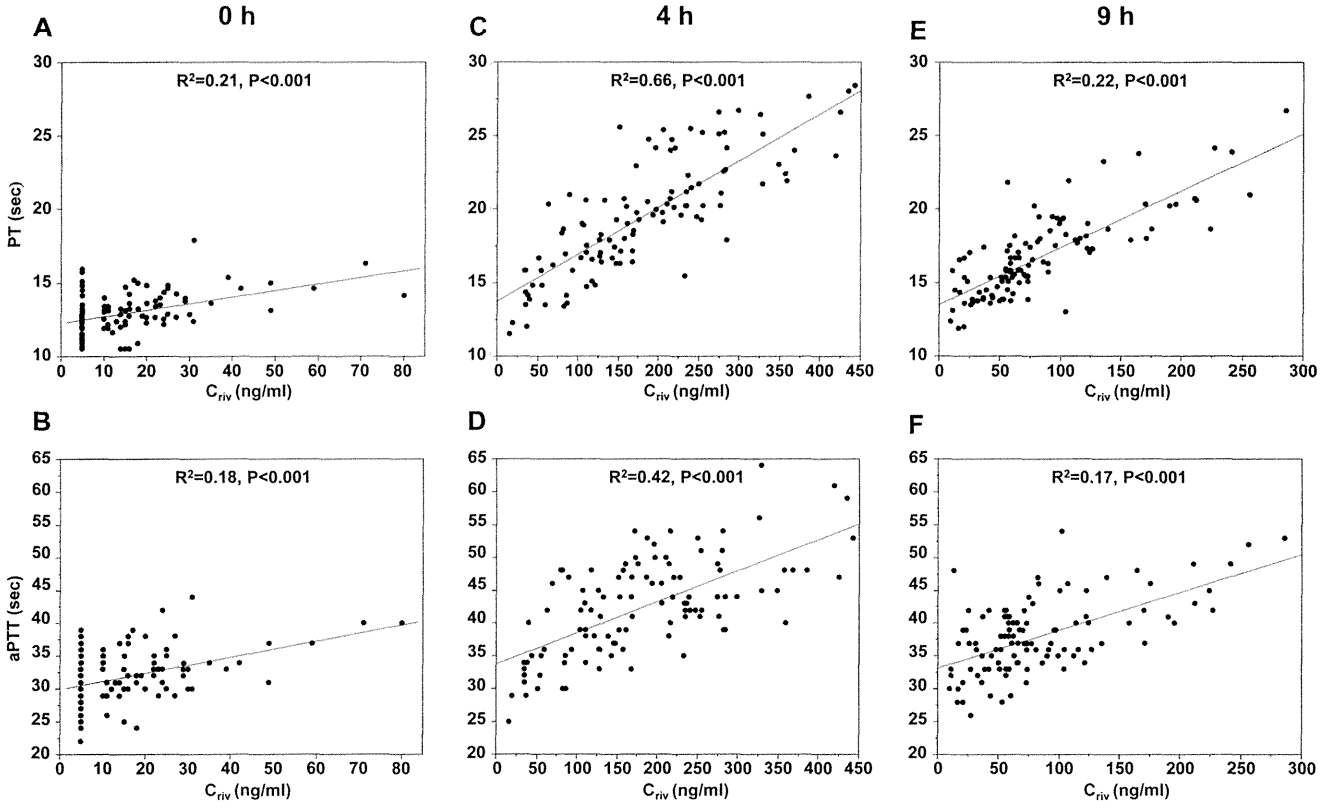


Figure 2. Correlations of estimated rivaroxaban concentration (C_{riv}) with PT (sec) and aPTT (sec) at 0 h (A, B), 4 h (C, D), and 9 h (E, F).

doi:10.1371/journal.pone.0113641.g002

dosage (P=0.029), and time from stroke/TIA onset to blood sampling (P=0.010) were identified as variables with P<0.20 by the preceding analysis for the linear mixed-effect model. Table 3 provides the adjusted estimates and 95% confidence intervals for the linear mixed-effect model. The results showed that diabetes mellitus (P=0.029), time from stroke/TIA onset to blood sampling (P=0.047), and tablet crushing (P<0.001) were significantly associated with C_{riv}.

Discussion

In the present study, the outcomes of conventional clotting tests and anti-factor Xa chromogenic assays in Japanese stroke patients taking rivaroxaban were evaluated to assess the anticoagulation intensity of rivaroxaban and explore its determinant factors. The anti-factor Xa chromogenic assay has showed acceptable accuracy and precision for quantitative measurements of rivaroxaban exposure, using rivaroxaban calibrators. The first major finding of this study was that C_{riv} at 4 h, indicating nearly peak concentration, was relatively low as compared with the maximum C_{riv} values in the ROCKET AF and J-ROCKET AF trials. The second major finding was that tablet crushing decreased anticoagulation intensity.

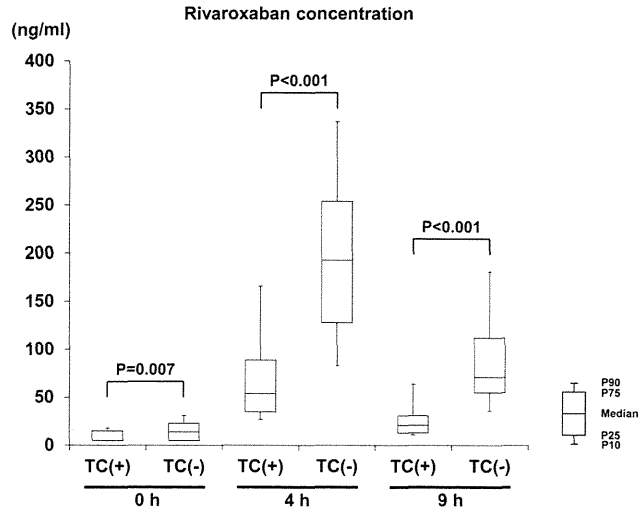


Figure 3. Comparison of rivaroxaban concentrations between groups with tablet crushing [TC (+)] and those without [TC (−)]. TC indicates tablet crushing.

doi:10.1371/journal.pone.0113641.g003

Since stroke patients are often aged and often have renal dysfunction [14, 15], lower dosages of NOACs tend to be chosen for such patients. In particular, special low dosages of rivaroxaban are recommended in Japan. Thus, we had a concern that C_{riv} in Japanese stroke patients was much lower than C_{riv} from global data. On the other hand, by transiently worsened renal function in the acute stroke setting, there was also a concern about accidental elevation of C_{riv}. According to exposure simulations performed in patients included in the ROCKET AF and

Table 3. Linear mixed-effect model to determine variables that influence rivaroxaban concentration.

Variable		Adjusted Estimate (95%CI)	P value
Congestive heart failure	No	Reference	0.482
	Yes	0.07 (−0.11 to 0.23)	
Diabetes mellitus	No	Reference	0.029
	Yes	0.13 (0.01 to 0.25)	
NIHSS score, per 1 point		−0.01(−0.02 to 0.01)	0.346
Rivaroxaban dosage	15 mg QD	Reference	0.146
	10 mg QD	−0.08 (−0.19 to 0.03)	
Tablet crushing	No	Reference	<0.001
	Yes	−0.43 (−0.60 to −0.26)	
Time from stroke/TIA onset to blood sampling, per day		−0.02 (−0.03 to 0.01)	0.047
Time points of blood sampling	0 h	Reference	
	4 h	1.13 (1.06 to 1.20)	<0.001
	9 h	0.29 (0.22 to 0.37)	<0.001

NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

doi:10.1371/journal.pone.0113641.t003

J-ROCKET AF trials, the maximum C_{riv} in Japanese patients with 15 mg QD (mean 249 ng/mL, J-ROCKET AF) was identical with that in non-Japanese patients with 20 mg QD (mean 249 ng/mL, ROCKET AF), and the maximum C_{riv} in Japanese with 10 mg QD (mean 168 ng/mL) was lower than that in non-Japanese with 15 mg QD (mean 229 ng/mL) [4]. These levels were still higher than the mean C_{riv} at 4 h in the present patients (197 ng/mL for 15 mg QD, 163 ng/mL for 10 mg QD). A reason for the large difference in C_{riv} was inclusion of patients receiving crushed tablets in the present study, since the mean C_{riv} at 4 h only in the patients receiving uncrushed tablets showed smaller differences from previous data (207 ng/mL for 15 mg QD, 188 ng/mL for 10 mg QD).

Previous studies demonstrated an 18% decrease in maximum C_{riv} for the crushed tablets suspended in water and administered via an NG tube followed by a liquid meal, compared to that after the whole tablet [10, 16], and a 29% decrease in AUC and a 56% decrease in maximum C_{riv} when the granulate was directly released into the proximal small intestine immediately followed by food. Thus, absorption of rivaroxaban seems to be dependent on the site of drug release in the gastrointestinal tract [10]. Indeed, the manufacturer recommends avoiding administration of rivaroxaban directly into the proximal small intestine (e.g., feeding tube) and illustrates the administration of crushed tablets via an NG tube or gastric feeding tube as a special option if patients are unable to swallow whole tablets. However, the present differences in C_{riv} between patients receiving crushed tablets and those receiving whole tablets were more divergent (72% at 4 h) than the above-mentioned results. Since rivaroxaban tablets are small, practically insoluble in water, and need to be crushed and suspended in water instead of a simple suspension method when administered via an NG tube [10], drug loss in the grinding, sifting, and packaging processes or drug remaining in the syringe and NG tube may occur.

Another possible reason for the low C_{riv} in the present patients was that the data were based on fixed time-point measurements, not on consecutive measurements to identify the peak level. The timing of blood sampling at 4 h in the present study was determined based on the previous finding noted in the Methods [10]. However, 10% of the present patients showed higher C_{riv} at 9 h than at 4 h, suggesting that the peak concentration time could be delayed in the clinical setting of acute stroke care, probably because the patients are old and often have renal dysfunction. Additionally, a previous phase-1 study displayed minor double peaks in rivaroxaban concentration after receiving crushed tablets via NG tubes; the first peak occurring around 45 minutes, and the second one between 4 and 6 h [16]. Our sampling timing at 4 h may be the nadir of biphasic peaks.

Although reduced CrCl is the only criterion for selecting a low dosage of rivaroxaban (10 mg QD) in Japan, 14 patients without a reduced CrCl were also given a low dosage based on the judgments of the physicians in charge because they had a history of bleeding or were very old. Such judgments appeared to contribute to the present low C_{riv} values. In addition, some patients might show higher serum creatinine levels in the acute stage of stroke than usual due to

hypovolemia and potential damage by acute stroke. CrCl in such patients might return to higher levels within several days; that might be another cause of the present low C_{riv} values.

The present study showed a linear relationship between PT and C_{riv}, as was also shown in the J-ROCKET AF and ROCKET AF trials [4, 17]. The present study also showed a linear relationship between aPTT and C_{riv}, although the R^2 level was lower than that of PT, and most earlier publications showed that aPTT is less sensitive than PT for rivaroxaban exposure assessment [18, 19]. However, the aPTT and PT results should be carefully interpreted because their sensitivities depend on the reagents.

The unique point of the present study was that most of the studied patients were enrolled into the study soon after onset of stroke or TIA; such acute patients were excluded from the major clinical trials [5, 6, 7, 8, 9] and have been infrequently studied after the approval of clinical use of NOACs. Although the optimal timing for initiation of NOACs has not been established, none of 412 patients who began to take NOACs in acute stage of ischemic stroke/TIA did not develop intracranial hemorrhage during acute hospitalization in our ongoing multicenter observational SAMURAI-NVAF study (Toyoda K, et al: unpublished data). The limitations of the present study included a relatively small sample size and the poor estimation accuracy of the anti-Xa chromogenic assay for C_{riv} when the concentration is low, as well as the fixed-point measurement of anticoagulation intensity.

In conclusion, this is the first study of Japanese stroke patients examining the anticoagulation intensity of rivaroxaban. The impressive finding was that tablet crushing, required for dysphagic patients, who are common in stroke medicine, decreased rivaroxaban concentration. Thus, tablet crushing should be carefully considered. At the least, patients with CrCl $\geq$50 mL/min should not be given a lower dosage (10 mg QD) when they need tablet crushing.

Acknowledgments

The authors would like to thank Kanae Takahashi, MPH, and Toshimitsu Hamasaki, MPH, for advice on statistical analyses.

Author Contributions

Conceived and designed the experiments: TO. Performed the experiments: TO. Analyzed the data: TO. Contributed reagents/materials/analysis tools: TO AO TM. Wrote the paper: TO KT. Provided study supervision: KN KM.

References

1. **Hart RG, Pearce LA, Aguilar MI** (2007) Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 146: 857–67.

2. **Fuster V, Ryden LE, Cannom DS, Crijns HJ, Curtis AB, et al.** (2006) ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation-executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation). Eur Heart J. 27: 1979–2030.

3. **Perzborn E, Strassburger J, Wilmen A, Pohlmann J, Roehrig S, et al.** (2005) In vitro and in vivo studies of the novel antithrombotic agent BAY 59-7939–an oral, direct Factor Xa inhibitor. J Thromb Haemost. 3: 514–21.

4. **Kaneko M, Tanigawa T, Hashizume K, Kajikawa M, Tajiri M, et al.** (2013) Confirmation of model-based dose selection for a Japanese phase III study of rivaroxaban in non-valvular atrial fibrillation patients. Drug Metab Pharmacokinet. 28: 321–31.

5. **Hori M, Matsumoto M, Tanahashi N, Momomura S, J-ROCKET AF study investigators**, et al. **(2012) Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation – the J-ROCKET AF study –. Circ J. 76: 2104–11.**

6. **Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, et al.** (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 365: 883–91.

7. **Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, et al.** (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 361: 1139–51.

8. **Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, et al.** (2013) Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 369: 2093–104.

9. **Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, et al.** (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 365: 981–92.

10. Xarelto [package insert]. Bayer Schering Pharma AG; 2013.

11. **Samama MM, Martinoli JL, LeFlem L, Guinet C, Plu-Bureau G, et al.** (2010) Assessment of laboratory assays to measure rivaroxaban-an oral, direct factor Xa inhibitor. Thromb Haemost. 103: 815–25.

12. **Samama MM, Contant G, Spiro TE, Perzborn E, Rivaroxaban Anti-Factor Xa Chromogenic Assay Field Trial Laboratories**, et al. (2012) Evaluation of the anti-Factor Xa chromogenic assay for the measurement of rivaroxaban plasma concentrations using calibrators and controls. Thromb Haemost. 107: 379–87.

13. **Lange N, Laird NM** (1989) The effects of Covariance Structure on Variance Estimation in Balanced Growth-Curve Models. J Am Stat Assoc. 84: 241–7.

14. **Toyoda K** (2012) The cerebro-renal interaction in stroke neurology. Neurology. 78: 1898–9.

15. **Toyoda K** (2013) Cerebrorenal interaction and stroke. Contrib Nephrol. 179: 1–6.

16. **Moore KT, Vaidyanathan S, Damaraju CV, Fields LE** (2012) The relative bioavailability of single-dose rivaroxaban, a novel oral anticoagulant and a selective direct factor Xa inhibitor, administered orally (as a whole or crushed tablet) and via nasogastric tube (as a crushed tablet suspension). ACCP Annual Meeting [Abstract].

17. **Tanigawa T, Kaneko M, Hashizume K, Kajikawa M, Ueda H, et al.** (2013) Model-based dose selection for phase III rivaroxaban study in Japanese patients with non-valvular atrial fibrillation. Drug Metab Pharmacokinet. 28: 59–70.

18. **Dyke CK, Becker RC, Kleiman NS, Hochman JS, Bovill EG, et al.** (2002) First experience with direct Factor Xa inhibition in patients with stable coronary disease: a pharmacokinetic and pharmacodynamics evaluation. Circulation. 105: 2385–91.

19. **Samama MM, Gerotziafas GT, Elalamy I, Horellou MH, Conard J** (2002) Biochemistry and clinical pharmacology of new anticoagulant agents. Pathophysiol Haemost Thromb. 32: 218–24.

European Journal of Neurology 2014, 21: 411–418 doi:10.1111/ene.12294

Simple clinical predictors of stroke outcome based on National Institutes of Health Stroke Scale score during 1-h recombinant tissue-type plasminogen activator infusion

M. Osaki[a], F. Miyashita[a], M. Koga[b], M. Fukuda[a], Y. Shigehatake[a], K. Nagatsuka[c], K. Minematsu[a] and K. Toyoda[a]

[a]*Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Osaka;* [b]*Division of Stroke Care Unit, National Cerebral and Cardiovascular Center, Osaka; and* [c]*Department of Neurology, National Cerebral and Cardiovascular Center, Osaka, Japan*

Keywords:
acute stroke, neurological improvement, outcomes, recombinant tissue plasminogen activator, thrombolysis

Received 10 April 2013
Accepted 23 September 2013

Background and purpose: An index for predictors of stroke outcome was determined based on the National Institutes of Health Stroke Scale (NIHSS) scores during 1-h intravenous administration of recombinant tissue-type plasminogen activator (rt-PA).

Methods: Stroke patients with baseline NIHSS score ≥8 and occlusion at the internal carotid or middle cerebral arteries (ICA, MCA) were retrospectively studied from a prospective single-center registry. NIHSS scores and inverse change from baseline scores (ΔNIHSS) were assessed at 30 min and 1 h after rt-PA infusion. Patients were divided into two groups according to arterial occlusion sites: group P, ICA or proximal M1; and group D, distal M1 or M2. A modified Rankin Scale score of 2–6 at 3 months was defined as an unfavorable outcome.

Results: In all 108 patients, the cutoff NIHSS score predicting unfavorable outcome was ≥12 and cutoff ΔNIHSS scores were ≤2 at both 30 min and 1 h. In group P (n = 36), the cutoff NIHSS score was ≥14 at both 30 min and 1 h and cutoff ΔNIHSS scores were ≤1 at 30 min and ≤2 at 1 h. Unfavorable outcome was seen in all patients with $NIHSS_{1\ h} \geq 14$, $\Delta NIHSS_{30\ min} \leq 1$ and $\Delta NIHSS_{1\ h} \leq 2$. In group D ($n$ = 72), the cutoff NIHSS scores were ≥12 at both 30 min and 1 h, and cutoff ΔNIHSS scores were ≤2 at 30 min and ≤7 at 1 h; 90% of patients with unfavorable outcome showed $\Delta NIHSS_{1\ h} \leq 7$.

Conclusion: NIHSS and ΔNIHSS during 1-h rt-PA infusion seemed predictive of 3-month outcome when the site of arterial occlusion was identified prior to rt-PA.

Introduction

Intravenous (IV) recombinant tissue-type plasminogen activator (rt-PA) is recommended for acute ischaemic stroke within 4.5 h of symptom onset, although fewer than half of the patients return to a completely independent status by 3 months after treatment [1,2]. When IV rt-PA proves ineffective, additional endovascular thrombectomy using methods such as the MERCI Retriever, Penumbra System or newer retrievable stents has the potential to recanalize the occluded artery [3–7], although the clinical advantage of the thrombectomy over IV thrombolysis has not been proved in large trials [8–10]. Generally, the shorter time from onset to treatment is related to better outcomes in patients treated with either IV rt-PA or endovascular therapy [11–13]. However, the optimal timing for additional thrombectomy is unclear. Some patients have shown recovery from the initial deficits several hours after rt-PA therapy. However, waiting too long will miss the window of opportunity for optimal results of thrombectomy. Angiographic identification of residual arterial occlusion after rt-PA is a practical strategy for determining the timing of additional thrombectomy [4]. Determination of such timing based on symptomatic indicators, including a National Institutes of Health Stroke Scale (NIHSS) score, would be easier and more convenient than angiographic identification. Although several studies reported the contribution of changes in NIHSS scores within 24 h to outcomes after IV rt-PA [14–18], some determined the contribution of the change within 1 h

Correspondence: K. Toyoda, MD, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, 5-7-1 Fujishirodai, Suita, Osaka 565-8565, Japan (tel.: +81 6 6833 5012; fax: +81 6 6835 5267; e-mail: toyoda@ncvc.go.jp).

EUROPEAN JOURNAL OF NEUROLOGY
THE OFFICIAL JOURNAL OF THE EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES