Table 1. Baseline clinical characteristics

Baseline characteristics	Renal dysfunction (eGFR <60 ml/min/1.73 m^2) (n = 186)	No renal dysfunction (eGFR ≥60 ml/min/1.73 m^2) (n = 392)	p value
Male patients	113 (60.8)	259 (66.1)	0.227
Age, years	76.0 ± 9.8	69.2 ± 12.0	<0.001
Body mass index	22.7 ± 3.2	23.0 ± 3.4	0.397
Hypertension	137 (73.7)	219 (55.9)	<0.001
Diabetes mellitus	37 (19.9)	70 (17.9)	0.568
Dyslipidemia	35 (18.8)	89 (22.7)	0.329
Atrial fibrillation	97 (52.2)	148 (37.8)	0.001
Liver disease	8 (4.3)	9 (2.3)	0.194
Prior ischemic heart disease	37 (19.9)	37 (9.4)	<0.001
Prior ischemic stroke	39 (21.0)	62 (15.8)	0.129
Prior use of antithrombotic agents	92 (49.5)	125 (31.9)	<0.001
Systolic blood pressure, mm Hg	150 ± 20	151 ± 20	0.613
Diastolic blood pressure, mm Hg	80 ± 16	83 ± 15	0.077
Stroke subtype			
Large-artery atherosclerosis	24 (12.9)	65 (16.6)	0.141
Cardioembolism	128 (68.8)	236 (60.2)	
Lacune	5 (2.7)	23 (5.9)	
Other	29 (15.6)	68 (17.4)	
Internal carotid artery occlusion	29 (15.6)	59 (15.2)	0.902
Blood glucose, mmol/l	7.68 ± 2.77	7.61 ± 2.61	0.787
Hemoglobin A1c, %	5.8 ± 1.0	5.8 ± 1.1	0.995
Total cholesterol, mmol/l	4.68 ± 1.07	5.01 ± 1.01	<0.001
Triglyceride, mmol/l	1.30 ± 0.72	1.32 ± 0.95	0.809
HDL cholesterol, mmol/l	1.27 ± 0.36	1.38 ± 0.40	0.003
LDL cholesterol, mmol/l	2.83 ± 0.88	3.01 ± 0.87	0.043
Time to treatment onset, min	145 (121–167)	146 (122–166)	0.991
Admission NIHSS score	13 (7–19)	12 (7.25–18)	0.423

Numbers of patients (%) are shown except otherwise indicated; data are means ± SD or medians (IQR).

patients belonged to stage 3, 15 (2.6%) to stage 4, and 8 (1.4%) to stage 5. Four patients with stage 5 were on maintenance hemodialysis.

The patients with renal dysfunction were older ($p < 0.001$) and more commonly had hypertension ($p < 0.001$), atrial fibrillation ($p = 0.001$), prior ischemic heart disease ($p < 0.001$), and prior use of antithrombotic agents ($p < 0.001$) than patients without renal dysfunction (table 1). Serum total cholesterol ($p < 0.001$), HDL cholesterol ($p = 0.003$), and LDL cholesterol ($p = 0.043$) levels were lower in patients with renal dysfunction than in those without. NIHSS scores were not significantly different between patients with renal dysfunction and those without immediately before [median (interquartile range, IQR); 13 (7–19) vs. 12 (7.25–18), $p = 0.423$] and 24 h after IV rt-PA [9 (3–18) vs. 7 (3–15), $p = 0.070$; fig. 1a].

Any ICH [51 (27.4%) vs. 65 patients (16.6%), $p = 0.004$] as well as symptomatic ICH within 36 h from IV rt-PA therapy [15 (8.1%) vs. 10 patients (2.6%), $p = 0.004$], was more common in the patients with renal dysfunction than in those without. After multivariate logistic regression analysis, renal dysfunction was significantly related to both any ICH (odds ratio, OR, 1.81, 95% confidence interval, CI, 1.16–2.84, $p = 0.009$) and symptomatic ICH (2.64, 1.10–6.56, $p = 0.031$; table 2). When the value of eGFR (a continuous variable) was used instead of eGFR <60 ml/min/1.73 m^2 (a categorical variable) as an indicator of renal dysfunction, it was related to any ICH (OR 0.89, 95% CI 0.80–0.99 per 10-ml/min/1.73 m^2 increase, $p = 0.029$) but not symptomatic ICH (0.89, 0.73–1.08, $p = 0.231$).

At 3 months, the patients with renal dysfunction had higher mRS scores than those without [median (IQR); 3

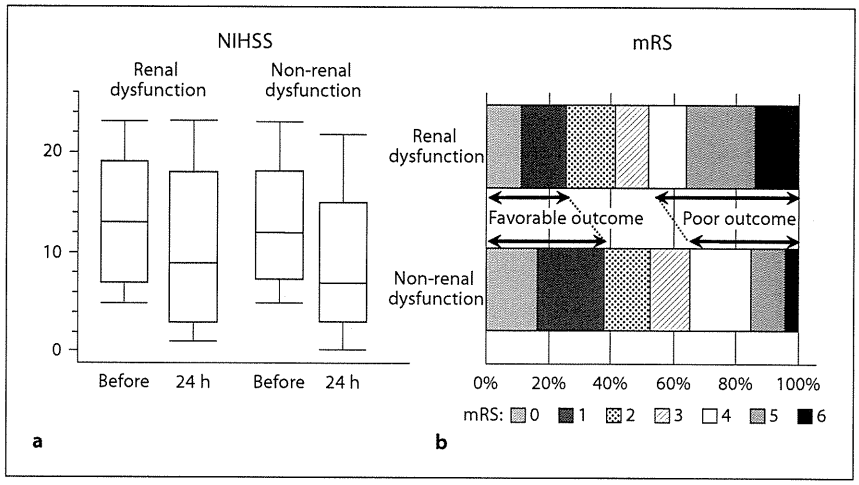

Fig. 1. Neurological deficits and outcome of patients with and without renal dysfunction. NIHSS score just before and 24 h after IV rt-PA therapy (**a**) and mRS score at 3 months (**b**) in patients with and without renal dysfunction. **a** Horizontal lines in boxes = Median NIHSS score; boxes = IQR; whiskers = upper and lower 90% ranges.

Table 2. Characteristics associated with ICH within 36 h

Characteristics	Any ICH			Symptomatic ICH		
	OR	95% CI	p value	OR	95% CI	p value
Male	1.12	0.71–1.78	0.638	1.99	0.74–6.32	0.201
Age (per year)	0.99	0.97–1.01	0.423	1.00	0.96–1.04	0.868
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	1.81	1.16–2.84	0.009	2.64	1.10–6.56	0.031
Atrial fibrillation	1.93	1.24–3.01	0.004	–	–	–
Liver disease	1.53	0.40–4.79	0.488	–	–	–
Prior use of antithrombotic agents	–	–	–	4.31	1.72–12.06	0.003
Blood glucose (per mmol/l)	1.06	0.98–1.14	0.153	1.11	0.96–1.26	0.126
Triglyceride (per mmol/l)	–	–	–	1.00	0.99–1.01	0.174
Admission NIHSS score (per point)	1.03	0.99–1.06	0.069	–	–	–

– = The variable was not included after the backward selection procedure.

Table 3. Characteristics associated with outcome at 3 months

Characteristics	Favorable outcome (mRS 0–1)			Poor outcome (mRS 4–6)			Death		
	OR	95% CI	p value	OR	95% CI	p value	OR	95% CI	p value
Male	1.14	0.74–1.76	0.545	0.84	0.55–1.29	0.430	0.68	0.32–1.48	0.331
Age (per year)	0.97	0.96–0.99	0.005	1.04	1.02–1.06	<0.001	1.01	0.97–1.05	0.718
Renal dysfunction (eGFR <60 ml/min/1.73 m^2)	0.70	0.44–1.09	0.114	1.55	1.01–2.38	0.046	2.94	1.38–6.42	0.006
Prior ischemic heart disease	–	–	–	–	–	–	4.33	1.84–10.05	<0.001
Internal carotid artery occlusion	0.24	0.10–0.51	<0.001	6.07	3.38–11.39	<0.001	4.32	2.00–9.36	<0.001
Blood glucose (per mmol/l)	0.91	0.84–0.99	0.024	1.08	1.01–1.17	0.033	1.17	1.04–1.31	0.007
Admission NIHSS score (per point)	0.91	0.88–0.94	<0.001	1.11	1.08–1.15	<0.001	1.09	1.04–1.15	<0.001

– = The variable was not included after the backward selection procedure. For favorable outcome analysis, patients with premorbid mRS score 2–3 were excluded.

(1–5) vs. 2 (1–4), $p < 0.001$; fig. 1b]. Twenty-five patients (13.4%) with renal dysfunction had died; of these, 5 died of stroke, 6 of heart disease (4 heart failure, 1 myocardial infarction, and 1 infectious endocarditis), 6 of severe infection (3 sepsis and 3 pneumonia), and 8 of unknown causes. In contrast, 15 patients (3.8%, $p < 0.001$) without renal dysfunction had died; of these, 9 died of stroke, 2 of pneumonia, and 4 of unknown causes. Similarly, favorable outcome was less common [48 (25.8%) vs. 149 patients (38.0%), $p = 0.004$], and poor outcome was more common [89 (47.9%) vs. 136 patients (34.7%), $p = 0.003$] in patients with renal dysfunction than in those without. After multivariate logistic regression analysis, renal dysfunction was significantly related to poor outcome (OR 1.55, 95% CI 1.01–2.38, $p = 0.046$) and mortality (OR 2.94, 95% CI 1.38–6.42, $p = 0.006$), although it was not related to favorable outcome (OR 0.70, 95% CI 0.44–1.09, $p = 0.114$; table 3). When the value of eGFR was used instead, it was significantly related to mortality (OR 0.81, 95% CI 0.67–0.96 per 10-ml/min/1.73 m^2 increase, $p = 0.020$), but not to favorable outcome (OR 1.09, 95% CI 0.99–1.20, $p = 0.081$) or poor outcome (OR 0.95, 95% CI 0.86–1.04, $p = 0.268$).

Discussion

In this observational study, we determined the influence of renal dysfunction on early ICH and the long-term outcome of ischemic stroke patients receiving IV rt-PA therapy. The major finding was that renal dysfunction, defined as reduced eGFR (<60 ml/min/1.73 m^2), which was calculated using the admission creatinine level, was related to any ICH and symptomatic ICH within 36 h, as well as poor outcome (mRS 4–6) and death at 3 months, although it was not related to favorable outcome (mRS 0–1).

According to the result of the largest postmarketing surveillance on rt-PA, the Safe Implementation of Thrombolysis in Stroke-Monitoring Study [21], advanced age, body weight, atrial fibrillation, high systolic blood pressure, hyperglycemia, admission NIHSS score, and current infarction on baseline imaging scans were associated with symptomatic ICH. In addition, advanced age, male sex, use of antiplatelet agents other than aspirin, congestive heart failure, higher diastolic blood pressure, hyperglycemia, higher NIHSS score, current infarction, and premorbid dependency were related to death at 3 months. Similar results have been reported in several other studies [22–26]. However, these studies did not assess renal dysfunction as a potential factor affecting stroke outcome. The present study is unique in that renal dysfunction was included as a potential factor and was proven to be associated with patient outcome after rt-PA.

Alteplase is metabolized by the liver, and liver function affects the half-life of alteplase [27]. In this study, liver disease was not associated with stroke outcome. In contrast, renal dysfunction might not prolong the half-life of alteplase. For example, the plasma concentration-time profile of alteplase was not altered after bilateral nephrectomy in rat models [28].

Renal dysfunction is a bystander of stroke, since it is associated with traditional vascular risk factors, including aging, hypertension, diabetes mellitus, dyslipidemia, and smoking [29]. In addition, renal dysfunction is now known to be an independent predictor for stroke [1, 2, 5, 30, 31], partly via nontraditional vascular risk factors, e.g. inflammatory factors, and homocysteinemia. However, the effect of these nontraditional risk factors on stroke outcome has not been clarified, in particular after rt-PA. In patients with acute stroke not receiving IV rt-PA, albuminuria was independently associated with hemorrhagic transformation [32]. Since ICH is a major cause of poor outcome for thrombolysed patients, renal dysfunction may affect chronic outcome after rt-PA via increasing ICH risk. Moreover, renal dysfunction might impair endothelial release of t-PA [33], and increase plasminogen activator inhibitor-1 activity [34] and plasma levels of lipoprotein(a) [35]; these abnormalities might obstruct the reperfusion phenomenon and worsen stroke outcome after IV rt-PA.

An interesting finding regarding the patients who died was that indirect death other than stroke was common as the cause of death for patients with renal dysfunction, though direct stroke death accounted for most of the causes of death for patients without renal dysfunction. This finding suggests that patients with renal dysfunction often had heart problems and susceptibility to infection, developed dependency and died due to non-stroke complications.

Certain limitations need to be considered prior to interpretation of the present results. First, patients who did not receive IV rt-PA were not included in this study. Thus, the influence of renal dysfunction on stroke outcome could not be compared between patients who were treated with rt-PA and those who were not. Second, renal dysfunction was correlated with older age, hypertension, atrial fibrillation, prior ischemic heart disease, and prior use of antithrombotic agents, and this multicolineality may inflate the variances of the parameter estimates. Thus, the present association of renal dysfunction with outcome measures after multivariate analyses may be

overestimated to some extent. Third, eGFR was not measured prior to stroke onset, and therefore eGFR may have been affected by stroke. Fourth, eGFR was calculated using admission creatinine levels, which may have been impaired by acute stroke effects. Repeated assessment in the chronic stroke stage is needed to ascertain that the present patients with reduced eGFR have chronic kidney disease. Fifth, urinary albumin was not measured. Generally, urinary albumin increases during acute ischemic stroke [36]. Finally, the present results based on low-dose rt-PA therapy (0.6 mg/kg) may not be applicable to the regular dose therapy (0.9 mg/kg).

In conclusion, reduced eGFR based on the admission creatinine level was predictive of an unfavorable outcome after IV rt-PA in acute stroke patients. In patients with renal dysfunction, additional therapeutic strategies to improve the efficacy of rt-PA are needed.

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References

1 Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, Wareham NJ: Microalbuminuria and stroke in a British population: the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study. J Intern Med 2004;255:247–256.
2 Ninomiya T, Kiyohara Y, Kubo M, Tanizaki Y, Doi Y, Okubo K, Wakugawa Y, Hata J, Oishi Y, Shikata K, Yonemoto K, Hirakata H, Iida M: Chronic kidney disease and cardiovascular disease in a general Japanese population: the Hisayama study. Kidney Int 2005; 68:228–236.
3 Guerrero-Romero F, Rodriguez-Moran M: Proteinuria is an independent risk factor for ischemic stroke in non-insulin-dependent diabetes mellitus. Stroke 1999;30:1787–1791.
4 De Leeuw PW, Thijs L, Birkenhager WH, Voyaki SM, Efstratopoulos AD, Fagard RH, Leonetti G, Nachev C, Petrie JC, Rodicio JL, Rosenfeld JJ, Sarti C, Staessen JA: Prognostic significance of renal function in elderly patients with isolated systolic hypertension: results from the Syst-Eur trial. J Am Soc Nephrol 2002;13:2213–2222.
5 Koren-Morag N, Goldbourt U, Tanne D: Renal dysfunction and risk of ischemic stroke or TIA in patients with cardiovascular disease. Neurology 2006;67:224–228.
6 Klausen KP, Scharling H, Jensen JS: Very low level of microalbuminuria is associated with increased risk of death in subjects with cardiovascular or cerebrovascular diseases. J Intern Med 2006;260:231–237.
7 MacWalter RS, Wong SY, Wong KY, Stewart G, Fraser CG, Fraser HW, Ersoy Y, Ogston SA, Chen R: Does renal dysfunction predict mortality after acute stroke? A 7-year follow-up study. Stroke 2002;33:1630–1635.
8 Yahalom G, Schwartz R, Schwammenthal Y, Merzeliak O, Toashi M, Orion D, Sela BA, Tanne D: Chronic kidney disease and clinical outcome in patients with acute stroke. Stroke 2009;40:1296–1303.
9 Tsagalis G, Akrivos T, Alevizaki M, Manios E, Stamatellopoulos K, Laggouranis A, Vemmos KN: 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.
10 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;71:1548–1550.
11 Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Minematsu K: Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) Study Investigators. Routine use of intravenous low-dose rt-PA in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. Stroke 2009; 40:3591–3595.
12 Nezu T, Koga M, Kimura K, Shiokawa Y, Nakagawara J, Furui E, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Naganuma M, Minematsu K, Toyoda K: Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA: SAMURAI rt-PA Registry. Neurology 2010;75:555–561.
13 Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, Shinohara Y, Japan Alteplase Clinical Trial (J-ACT) Group: Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). Stroke 2006; 37:1810–1815.
14 Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd: 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.
15 Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, Yamagata K, Tomino Y, Yokoyama H, Hishida A, on behalf of the collaborators developing the Japanese equation for estimated GFR: Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–992.
16 National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39:S1–S266.
17 The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995;333:1581–1587.

18 Kwiatkowski TG, Libman RB, Frankel M, Tilley BC, Morgenstern LB, Lu M, Broderick JP, Lewandowski CA, Marler JR, Levine SR, Brott T: Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. N Engl J Med 1999;340:1781–1787.
19 The NINDS t-PA Stroke Study Group: Generalized efficacy of t-PA for acute stroke. Subgroup analysis of the NINDS t-PA Stroke Trial. Stroke 1997;28:2119–2125.
20 Frankel MR, Morgenstern LB, Kwiatkowski T, Lu M, Tilley BC, Broderick JP, Libman R, Levine SR, Brott T: Predicting prognosis after stroke: a placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial. Neurology 2000;55:952–959.
21 Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Dávalos A, Erilä T, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Köhrmann M, Larrue V, Lees KR, Machnig T, Roine RO, Toni D, Vanhooren G, Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy Investigators: Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). Stroke 2008;39:3316–3322.
22 Demchuk AM, Morgenstern LB, Krieger DW, Linda Chi T, Hu W, Wein TH, Hardy RJ, Grotta JC, Buchan AM: Serum glucose level and diabetes predict tissue plasminogen activator-related intracerebral hemorrhage in acute ischemic stroke. Stroke 1999;30:34–39.
23 Kidwell CS, Saver JL, Carneado J, Sayre J, Starkman S, Duckwiler G, Gobin YP, Jahan R, Vespa P, Villablanca JP, Liebeskind DS, Vinuela F: Predictors of hemorrhagic transformation in patients receiving intra-arterial thrombolysis. Stroke 2002;33:717–724.
24 Larrue V, von Kummer RR, Müller A, Bluhmki E: Risk factors for severe hemorrhagic transformation in ischemic stroke patients treated with recombinant tissue plasminogen activator: a secondary analysis of the European-Australasian Acute Stroke Study (ECASS II). Stroke 2001;32:438–441.
25 Counsell C, Dennis M: Systematic review of prognostic models in patients with acute stroke. Cerebrovasc Dis 2001;12:159–170.
26 Tanne D, Kasner SE, Demchuk AM, Koren-Morag N, Hanson S, Grond M, Levine SR: Markers of increased risk of intracerebral hemorrhage after intravenous recombinant tissue plasminogen activator therapy for acute ischemic stroke in clinical practice: the Multicenter rt-PA Stroke Survey. Circulation 2002;105:1679–1685.
27 Korninger C, Stassen JM, Collen D: Turnover of human extrinsic (tissue-type) plasminogen activator in rabbits. Thromb Haemost 1981;46:658–661.
28 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;21:236–241.
29 Uhlig K, Levey AS, Sarnak MJ: Traditional cardiac risk factors in individuals with chronic kidney disease. Semin Dial 2003;16:118–127.
30 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY: Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–1305.
31 McCullough PA, Li S, Jurkovitz CT, Stevens LA, Wang C, Collins AJ, Chen SC, Norris KC, McFarlane SI, Johnson B, Shlipak MG, Obialo CI, Brown WW, Vassalotti JA, Whaley-Connell AT, Kidney Early Evaluation Program Investigators: CKD and cardiovascular disease in screened high-risk volunteer and general populations: the Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999–2004. Am J Kidney Dis 2008;51:S38–S45.
32 Rodriguez-Yanez M, Castellanos M, Blanco M, Millan M, Nombela F, Sobrino T, Lizasoain I, Leira R, Serena J, Davalos A, Castillo J: Micro- and macroalbuminuria predict hemorrhagic transformation in acute ischemic stroke. Neurology 2006;67:1172–1177.
33 Hrafnkelsdottir T, Ottosson P, Gudnason T, Samuelsson O, Jern S: Impaired endothelial release of tissue-type plasminogen activator in patients with chronic kidney disease and hypertension. Hypertension 2004;44:300–304.
34 Kamgar M, Nobakhthaghighi N, Shamshirsaz AA, Estacio RO, McFann KK, Schrier RW: Impaired fibrinolytic activity in type II diabetes: correlation with urinary albumin excretion and progression of renal disease. Kidney Int 2006;69:1899–1903.
35 Kronenberg F, Utermann G, Dieplinger H: Lipoprotein(a) in renal disease. Am J Kidney Dis 1996;27:1–25.
36 Slowik 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.

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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

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Key Words
Acute ischemic stroke · Cerebral infarction · Chronic kidney disease · End-stage renal disease · Hemodialysis · Renal dysfunction · rt-PA · Thrombolysis

Abstract
Background: To examine the therapeutic effect of intravenous recombinant tissue plasminogen activator (rt-PA) therapy for stroke patients receiving maintenance hemodialysis (HD). ***Methods:*** Of 600 stroke patients receiving intravenous rt-PA using 0.6 mg/kg alteplase who were enrolled in a multicenter observational study in Japan, 4 patients (3 men, 64–77 years old) on maintenance HD were studied. ***Results:*** The primary kidney disease requiring HD was glomerulonephritis in 2 patients, diabetic nephropathy in 1, and undetermined in 1. The duration of HD ranged between 1.2 and 28 years. Three patients developed stroke on the day of HD, including 1 during HD and another just after HD. All patients had stroke in the carotid arterial territory. Pretreatment NIH Stroke Scale scores ranged between 4 and 20, and decreased by 2–5 points at 7 days. One patient needed intravenous antihypertensive therapy before rt-PA; he developed an ectopic cortical hematoma and intraventricular hemorrhage after rt-PA. The other 3 did not develop hemorrhagic complications. The modified Rankin Scale score at 3 months was 0 in 1 patient, 2 in 2 patients, and 4 in 1 patient. ***Conclusions:*** rt-PA therapy for stroke patients receiving maintenance HD might improve the stroke outcome. Ectopic hematoma was a unique complication in our case series.

Introduction

Patients receiving hemodialysis (HD) have a higher risk of stroke than the general population [1], and they often develop stroke during or just after HD while they remain in the clinic [2]. Thus, HD patients might have a high opportunity to receive urgent therapies for stroke, including intravenous (IV) recombinant tissue plasminogen activator (rt-PA). HD itself is not a contraindication to IV rt-PA in several guidelines, but heparinization is. In addition, severe renal damage appears to affect the outcome after rt-PA [3, 4].

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Table 1. Baseline characteristics and physiological and laboratory data on admission

	Patient 1 female	Patient 2 male	Patient 3 male	Patient 4 male
Age, years	74	77	68	64
Body mass index	17.6	21.1	20.3	27.9
Primary kidney disease	glomerulonephritis	undetermined	diabetic nephropathy	glomerulonephritis
Duration of hemodialysis, years	28	2	1.2	24
Stage of hypertension [13]	high normal	stage I	stage I	stage II
Other vascular risk factors	atrial fibrillation[1]	sick sinus syndrome	diabetes mellitus	–
Vascular comorbidities	MI, silent brain infarct	angina pectoris	MI	–
Other comorbidities	hepatitis C virus carrier, hyperparathyroidism	–	meningioma (resected)	gastric cancer (resected)
Premorbid modified Rankin Scale score	0	0	0	0
Prior medication				
Antithrombotics	aspirin	aspirin	none	none
Antihypertensives (vasodilator)	ISDN	torasemide, ISDN	none	nifedipine, limaprost
Antidiabetics	none	none	insulin	none
Physiological/laboratory data on admission				
Blood pressure, mm Hg	202/83	165/81	150/86	218/98
Platelet count, /μl	254,000	175,000	140,000	124,000
Hemoglobin, g/dl	12.1	12.9	10.6	10.6
Prothrombin time (INR)	1.13	0.89	1.10	0.90
Activated partial thromboplastin time, s	43.5	26	36.4	32
Blood urea nitrogen, mmol/l	3.9	22.8	12.1	11.8
Creatinine, μmol/l	230	919	327	415
Blood glucose, mmol/l	5.7	10.5	12.7	5.0
Hemoglobin A_{1c}, %	4.3	5.3	5.9	not measured
Total cholesterol, mmol/l	3.29	4.12	4.17	4.25
Triglyceride, mmol/l	0.59	1.24	1.50	0.64
HDL cholesterol, mmol/l	1.14	1.48	0.83	1.40
LDL cholesterol, mmol/l	1.89	2.07	2.64	2.41

INR = International normalized ratio; ISDN = isosorbide dinitrate; MI = myocardial infarction.
[1] Identified during acute hospitalization after stroke onset.

We have reported the effects of IV rt-PA given to stroke patients with renal dysfunction using the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry [4]. Reduced estimated glomerular filtration rate <60 ml/min/1.73 m^2 on admission was independently associated with intracerebral hemorrhage (ICH) within 36 h after rt-PA and unfavorable functional outcome or death at 3 months. The results suggest that end-stage renal disease (ESRD) is also associated with poor outcome after rt-PA, although, to the best of our knowledge, this issue has never been examined.

The aim of this study was to determine the effect of IV rt-PA therapy in stroke patients on maintenance HD using the same registry.

Patients and Methods

The SAMURAI rt-PA Registry had a multicenter, hospital-based, retrospective, observational, cohort design [4–6]. A total of 600 consecutive patients with acute ischemic stroke receiving alteplase at 0.6 mg/kg (the recommended dose in Japanese guidelines and the approved labeling) from October 2005 through July 2008 were registered. From the registry, ESRD patients receiving maintenance HD or peritoneal dialysis were studied. The local ethics committee approved the research protocol. Baseline characteristics, physiological and laboratory data on admission, stroke features, and outcomes were assessed for each patient. Diffusion-weighted MRI (DWI) and MRA were performed before rt-PA infusion in addition to head CT. Early ischemic change was assessed using the Alberta Stroke Program Early CT Score (ASPECTS) [6].

Results

Of the 600 patients, none were on peritoneal dialysis and 4 (0.7%, 3 men, 64–77 years old) were undergoing maintenance HD before IV rt-PA therapy. These 4 patients were studied.

Baseline characteristics and physiological and laboratory data on admission are listed in table 1. In brief, the primary kidney disease responsible for HD was glomeru-

Table 2. Stroke features and outcomes

	Patient 1	Patient 2	Patient 3	Patient 4
Timing of stroke onset	just after HD	non-HD day	2 h after HD	during HD
Major neurological signs	aphasia, unilateral spatial neglect, right hemiparesis	unilateral spatial neglect, left hemiparesis	aphasia, right facial palsy	aphasia
ASPECTS on CT	10	9	10	10
ASPECTS on DWI	9	8	9	10
Site of arterial occlusion	M2	ICA	undetectable	undetectable
Stroke territory	left carotid	right carotid	left carotid	left carotid
Stroke etiology	cardioembolism	cardioembolism	undetermined	undetermined
Onset to rt-PA time, min	130	139	150	166
Pre-rt-PA antihypertensives	none	none	none	IV nicardipine
Antithrombotic therapy after rt-PA	IV unfractionated heparin 24 h after rtPA followed by warfarin	IV argatroban 24 h after rtPA followed by warfarin	IV unfractionated heparin 24 h after rtPA followed by aspirin	IV unfractionated heparin 48 h after rtPA followed by aspirin
Timing of restarting HD after rt-PA	20 h later	20 h later	2 days later	22 h later
Intracerebral hemorrhage during acute stage	absent	absent	absent	present (see fig. 2)
NIH stroke scale score				
Baseline	20	13	11	4
24 h after rt-PA	18	11	5	5
7 days after rt-PA	18	9	6	2
Modified Rankin Scale score at 3 months	4	2	2	0

ICA = Internal carotid artery.

lonephritis in 2 patients, diabetic nephropathy in 1, and undetermined in 1. The duration of HD ranged between 1.2 and 28 years. All patients had hypertension, and 2 were taking aspirin prior to stroke. Stroke features and outcomes are listed in table 2. One patient developed stroke during HD and another just after HD. All patients had stroke in the carotid arterial territory; 2 were due to cardioembolism and 2 were of undetermined mechanisms. In the latter 2, emboligenic diseases were not identified using transesophageal echocardiography and Holter ECG. For patient 4, hemodialytic procedure by itself may be a possible cause of stroke since he developed stroke during HD. One patient needed IV antihypertensive therapy just before rt-PA. Pretreatment NIH Stroke Scale scores ranged between 4 and 20 and decreased by 2–5 points at 7 days. No patients showed neurological deterioration. The modified Rankin Scale score at 3 months was 0 in 1 patient, 2 in 2 patients, and 4 in 1 patient.

Early ischemic changes on baseline DWI are shown in figure 1. Early ischemic changes were found in the left insular and frontal cortices in patient 1, the right basal ganglia and corona radiata extending to the insular cortex in patient 2, and the left basal ganglia and corona radiata in patient 3. DWI-ASPECTS in these patients ranged between 8 and 9. In patient 4, ischemic changes were not identified on the baseline DWI, and they were later detected as tiny scattered infarcts in the left cortex. This patient developed transient headache and vomited once, 1 h after rt-PA; CT revealed an ectopic hematoma in the left temporal lobe with the left intraventricular hemorrhage. This patient had IV heparin 48 h after rt-PA, and the hematoma no longer grew after that. The other 3 patients did not develop any intracranial or systemic hemorrhagic complications.

Discussion

In this observational study, 4 stroke patients with HD receiving IV rt-PA were reported. The major finding was that 3 patients had functional independence (modified Rankin Scale score ≤ 2) at 3 months, although ICH with transient headache occurred in 1 of these 3.

Stroke patients with ESRD are at a disadvantage for IV rt-PA for several reasons [7–9]. First, advanced diabetes, which is known to be associated with poor outcome after IV rt-PA, is frequent in ESRD patients. Second, ESRD patients often have hypertension resistance to

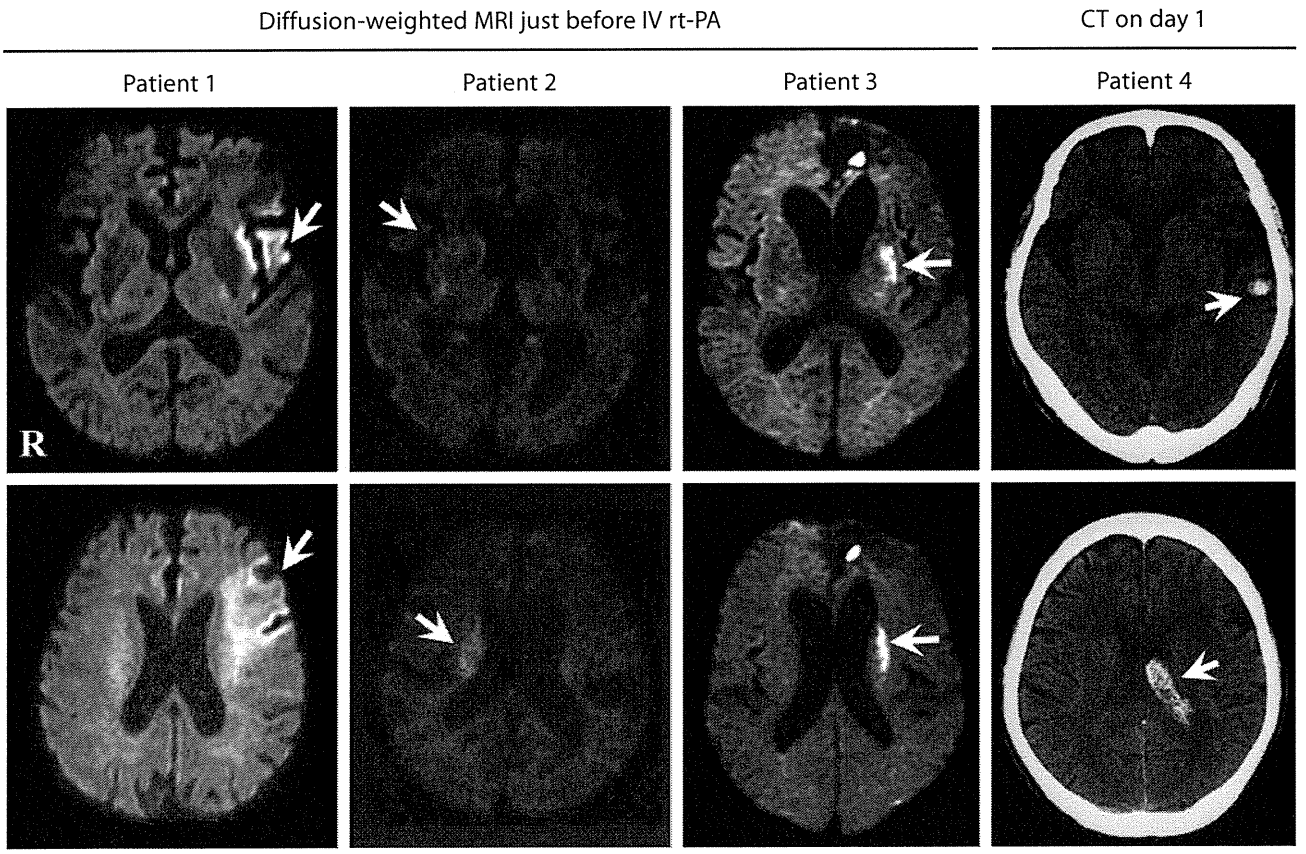

Fig. 1. DWI just before IV rt-PA therapy in patients 1–3, and CT on the day of thrombolysis in patient 4. Arrows show early ischemic changes or ectopic hemorrhage.

antihypertensives and other vascular risk factors and vascular comorbidities as predictors for a poor outcome. Third, blood surface interactions during HD lead to impairment of platelet function and a decrease in platelet number.

Another major disadvantage of ESRD patients is their high risk of ICH. Renal dysfunction is a predictor for hemorrhagic transformation in acute ischemic stroke with or without thrombolysis, presumably partly due to endothelial dysfunction related to renal dysfunction [4, 10]. Previous studies reported a relatively high percentage of ICH among total stroke in ESRD patients [1, 2]. In addition, HD is generally given three times per week using heparin as an anticoagulant, and the activated partial thromboplastin time often exceeds the normal range. A unique finding of the present study was the ectopic hematoma after rt-PA in patient 4. Since 19–35% of patients receiving HD had cerebral microbleeds documented on T_2*-weighted, gradient echo MRI [11, 12], such microbleeds might have grown to be an overt hematoma in this patient. Receiving rt-PA soon after stopping HD (although activated partial thromboplastin time returned to the normal range) and the high baseline blood pressure that required IV antihypertensive therapy may have triggered this ICH; the coexistence of such conditions may be a contraindication to rt-PA.

In spite of several disadvantages, 3 of the present 4 ESRD patients had functional independence 3 months after rt-PA. Since the study population was small, the efficacy and risk of IV rt-PA in ESRD patients could not be determined from this study alone. However, IV rt-PA does appear to be effective for some ESRD patients. A comparison between the patient having a poor outcome and the other patients suggests that initial neurological severity is a good predictor of outcome after rt-PA, as in general stroke patients. Moreover, these 4 patients, in-

cluding the 1 with a poor outcome, had relatively mild early ischemic changes.

Since thrombolysis for ESRD patients has been understudied, one often hesitates to use rt-PA for ESRD patients with hyperacute stroke. Furthermore, one might wonder if HD within 24 h of rt-PA is safe or not. The strength of this study is to report that IV rt-PA is a feasible strategy for ESRD patients for the first time as far as we know.

This study's limitations included its retrospective, observational design, the small number of ESRD patients, and the lack of data on patients who did not receive thrombolysis for stroke. Another limitation was that the present results, which were based on low-dose alteplase, may not be applicable to the regular-dose therapy (0.9 mg/kg).

Appendix

Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) Study Investigators:

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Investigators and Institutions: K. Kario, Jichi Medical University School of Medicine; J. Nakagawara, Nakamura Memorial Hospital; E. Furui, Kohnan Hospital; Y. Shiokawa, K. Nishiyama, Kyorin University School of Medicine; Y. Hasegawa, St Marianna University School of Medicine; S. Okuda, National Hospital Organization Nagoya Medical Center; H. Yamagami, Kobe City Medical Center General Hospital; K. Kimura, Kawasaki Medical School; Y. Okada, National Hospital Organization Kyushu Medical Center.

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Disclosure Statement

There are no conflicts of interest to disclose.

References

1 Iseki K, Fukiyama K, Okinawa Dialysis Study Group: Clinical demographics and long-term prognosis after stroke in patients on chronic haemodialysis. Nephrol Dial Transplant 2000;15:1808–1813.

2 Toyoda K, Fujii K, Fujimi S, Kumai Y, Tsuchimochi H, Ibayashi S, Iida M: Stroke in patients on maintenance hemodialysis: a 22-year single-center study. Am J Kidney Dis. 2005;45:1058–1066.

3 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;71:1548–1550.

4 Naganuma M, Koga M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Minematsu K, Toyoda K: Reduced estimated glomerular filtration rate is associated with stroke outcomes after intravenous rt-PA: the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA Registry. Cerebrovasc Dis 2011;31:123–129.

5 Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, Kimura K, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Minematsu K; Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement Study Investigators: Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients: general outcomes and prognostic factors from the SAMURAI register. Stroke 2009;40:3591–3595.

6 Nezu T, Koga M, Kimura K, Shiokawa Y, Nakagawara J, Furui E, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Nishiyama K, Naganuma M, Minematsu K, Toyoda K: Pre-treatment ASPECTS on DWI predicts 3-month outcome following rt-PA: SAMURAI rt-PA Registry. Neurology 2010;75:555–561.

7 Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Dávalos A, Erilä T, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Köhrmann M, Larrue V, Lees KR, Machnig T, Roine RO, Toni D, Vanhooren G; Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy Investigators: Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). Stroke 2008;39:3316–3322.

8 Aggarwal A, Kabbani SS, Rimmer JM, Gennari FJ, Taatjes DJ, Sobel BE, Schneider DJ: Biphasic effects of hemodialysis on platelet reactivity in patients with end-stage renal disease: a potential contributor to cardiovascular risk. Am J Kidney Dis 2002;40:315–322.

9 Horl MP, Horl WH: Hemodialysis-associated hypertension: pathophysiology and therapy. Am J Kidney Dis 2002;39:227–244.

10 Rodriguez-Yanez M, Castellanos M, Blanco M, Millan M, Nombela F, Sobrino T, Lizasoain I, Leira R, Serena J, Davalos A, Castillo J: Micro- and macroalbuminuria predict hemorrhagic transformation in acute ischemic stroke. Neurology 2006;67:1172–1177.

11 Yokoyama S, Hirano H, Uomizu K, Kajiya Y, Tajitsu K, Kusumoto K: High incidence of microbleeds in hemodialysis patients detected by T_2*-weighted gradient-echo magnetic resonance imaging. Neurol Med Chir 2005; 45:556–560.

12 Watanabe A: Cerebral microbleeds and intracerebral hemorrhages in patients on maintenance hemodialysis. J Stroke Cerebrovasc Dis 2007;16:30–33.

13 Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ: National Heart, Lung, Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: The JNC 7 Report. JAMA 2003;289:2560–2572.

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High level of plasma adiponectin in acute stroke patients is associated with stroke mortality

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ABSTRACT

We examined the association between plasma adiponectin (ADPN) levels and cardiovascular mortality in acute stroke patients. We enrolled 552 consecutive acute stroke patients. Measurements were made at baseline and the patients were followed prospectively. The primary endpoint was cardiovascular (stroke or ischemic heart disease) death and the secondary endpoint was all-cause death. During the median follow-up period of 17 months, 39 patients died, 15 being due to stroke. No patients died of ischemic heart disease. After adjustment for age, sex, presence of hypertension, diabetes mellitus, and hyperlipidemia, the highest tertile of ADPN level (>11.7 μg/ml) was associated with stroke mortality (hazard ratio: 6.55, 95% confidence interval: 1.73–24.8), but not with all-cause mortality (hazard ratio: 1.89, 95% confidence interval: 0.95–3.77). High levels of plasma ADPN can be a predictor of stroke mortality during the 17 months following an episode of acute stroke in patients.

1. Introduction

Adiponectin (ADPN) is a peptide hormone secreted by adipocytes, shown to have a number of beneficial effects, such as anti-atherosclerosis and anti-inflammatory properties, and improvement of insulin resistance in the general population [1]. A number of reports suggested that hypoadiponectinemia is associated with high incidence of coronary artery disease [2] and of ischemic stroke [3]. Hypoadiponectinemia in patients with ischemic stroke was associated with long-term mortality [4]. In an animal model, ADPN exhibited vascular protection and prevention of brain damage after acute ischemic injuries, which were mediated by an endothelial nitric oxide synthase-dependent mechanism [5]. In these studies, it was suggested that a low level of ADPN is a cardiovascular risk factor and the secretion or action of ADPN might reduce the risk of cardiovascular disease (CVD).

On the contrary, several recent studies demonstrated that a high level of ADPN was associated with risk of CVD events and mortality in the general population [6], as well as in patients with chronic heart failure [7–9], coronary artery disease [10], or chronic kidney disease [11]. ADPN was shown to improve insulin resistance, and administration of ADPN decreased body weight in animal model [12]. It is suggested that high levels of ADPN might act to promote wasting and cause body weight loss, which is associated with poor prognosis in CVD patients.

Thus, it is unclear whether ADPN plays a beneficial or a harmful role in CVD. The purpose of the present study was to examine the association between plasma ADPN levels and cardiovascular mortality in acute stroke patients.

2. Methods

2.1. Subjects

This was a single-center hospital-based prospective study that was approved by the Institutional Research and Ethics Committee of the National Cardiovascular Center, Japan. We registered 569 patients who were admitted to our Stroke Care Unit within 7 days of stroke onset from April 1, 2005 to August 31, 2007. Not counted in this group were patients with subarachnoid hemorrhage due to a ruptured aneurysm and those with massive brain hemorrhage requiring neurosurgical treatment. Because informed consent was not obtained from 17 patients, 552 patients (men/women = 367/185, median age, 71 years) were actually enrolled in the present study.

2.2. Baseline assessment

Brain CT, carotid ultrasonography, and ECG were performed for all patients at the time of admission. The cervico-cephalic arteries of all patients with ischemic stroke, who did not have an implanted pacemaker, were evaluated with magnetic resonance angiography in addition to carotid ultrasonography. Two-dimensional echocardiography

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was done to investigate a potential embolic source in patients with ischemic stroke. Morning blood samples were collected after overnight fasting for measurement of glucose, lipid levels, and ADPN, 2 weeks after the stroke onset. For 91 patients in this study, we confirmed that there were no significant differences between serum ADPN levels on admission and 2 weeks after the stroke onset (data not shown). Plasma glucose was measured by the glucose-oxidase method and plasma ADPN level was measured by enzyme-linked immunosorbent assay. Triglycerides, total cholesterol, low density lipoprotein cholesterol, high density lipoprotein cholesterol, and creatinine were measured enzymatically. Renal function was assessed by the estimated glomerular filtration rate (eGFR) formula using the equations for the Japanese population [13] from serum creatinine: eGFR (ml/min/1.73 m^2) = $194 \times (\text{serum creatinine})^{-1.094} \times (\text{age})^{-0.287} \times 0.739$ (for woman). Blood pressure was measured in all patients before discharge.

The diagnosis of stroke subtypes, such as atherothrombotic brain infarction (n = 90), lacunar infarction (n = 82), cardioembolic infarction (n = 130), other types of infarction (n = 123), and brain hemorrhage (n = 127), was made as previously described [14]. A diagnosis of atherothrombotic brain infarction was based on the presence of focal brain infarct(s) in the collection of evidence for occlusive lesions in the large cervical and intracranial arteries (either occlusion, ≥50% stenosis of the lumen diameter, or ulceration) determined by the clinical data. The diagnosis of lacunar infarction was made when a typical clinical syndrome was associated with a small infarct, <15 mm in diameter on CT, restricted to the territory of a perforating artery, and when no evidence of adjacent major artery occlusion or severe stenosis was found. Cardioembolic infarction was clinically diagnosed as described elsewhere [15]. If the patient had a combination of the above etiologies, or had undetermined etiologies (n = 72), if the stroke had other causes, such as arterial dissection, cerebral venous thrombosis (determined etiologies, n = 51), the index stroke was categorized to other types of infarction. The diagnosis of brain hemorrhage was based on CT findings.

National Institutes of Health Stroke Scale (NIHSS) scores were assessed on admission.

2.3. Patient follow-up

Patients were registered on the admission day. Information on vital status after the discharge from our hospital was obtained from medical charts of out-patient clinics or with telephone interview. All patients were followed up for at least 3 months until September, 2008. The primary endpoint was cardiovascular death (stroke and ischemic heart disease) and secondary endpoint was all-cause death.

2.4. Statistical analysis

Statistical analyses were performed using the SPSS 16.0J statistical package (SPSS, Inc., 2007). A value of $p<0.05$ was considered statistically significant.

ADPN levels were divided into tertiles (<6.8, 6.8–11.7, and >11.7 μg/ml). To determine the differences in clinical characteristics among the three groups of plasma ADPN levels or two groups of survivors and the dead, the χ^2 test, Student's t-test, Mann–Whitney U-test, ANOVA with Scheffe's F-test was used as appropriate. The correlations between plasma ADPN level and each cardiovascular risk factor were examined by a single regression analysis. Survival time was calculated from the date of admission to date of death. Survival rate was estimated by the Kaplan–Meier method and compared among the 3 groups by the log-rank test. The independent contribution of each factor to fatal events was estimated by the Cox proportional hazards models. Hazard ratios (HRs) for the incidence of fatal events were evaluated for to the highest tertile of ADPN level (>11.7 μg/ml) against the middle plus the lowest tertiles (≤11.7 μg/ml). Clinical covariates with the presence of hypertension, diabetes mellitus, and hyperlipidemia, were entered into the Cox proportional hazards models to adjust for potential confounders (Model 2). Subsequently, body mass index, eGFR, and NIHSS score on admission were added to covariates (Model 3).

3. Results

Median follow up period of this study was 17 months (range: 1–42 months). Plasma ADPN level of each stroke subtype were as follows: 9.3 ± 6.3 μg/ml in patients with atherothrombotic infarction, 9.0 ± 5.9 μg/ml in patients with lacunar infarction, 14.4 ± 11.1 μg/ml in patients with cardioembolic infarction, 10.5 ± 6.5 μg/ml in patients with other types of infarction, and 11.8 ± 8.6 μg/ml in patients with brain hemorrhage. Mean plasma ADPN level of patients with cerebral thrombosis (atherothrombotic infarction and lacunar infarction) was 9.2 ± 6.1 μg/ml, which was significantly lower than that in patients with cardioembolic infarction (14.4 ± 11.1 μg/ml, $p<0.001$).

Age, gender, body mass index, eGFR, frequencies of current smoker, diabetes, hyperlipidemia, median NIHSS score on admission, and the distribution of stroke subtypes were significantly different among the 3 levels of plasma ADPN (Table 1). In the lowest tertile, the larger number of younger patients and males was contained, and body mass index and eGFR were higher than those in the other tertiles. There were higher frequencies of current smokers, diabetes, and hyperlipidemia in the lowest tertile, and median NIHSS score on admission in the highest tertile was higher than those in the other 2 groups (Table 1). Plasma ADPN levels were significantly positively correlated with age ($r = 0.360$, $p<0.001$), HDL cholesterol ($r = 0.442$, $p<0.001$), and NIHSS score on admission ($r = 0.161$, $p<0.001$), and were negatively correlated with body mass index ($r = -0.346$, $p<0.001$), triglycerides ($r = -0.307$, $p<0.001$), and eGFR ($r = -0.203$, $p<0.001$).

From a total of 552 patients, 4 patients dropped out during the follow up period; 1 patient with atherothrombotic brain infarction, 1 patient with lacunar infarction, and 2 patients with other types of infarction. From the remaining 548 patients, 39 patients died, of which 15 patients died of stroke (3 patients died during hospitalization) during the median follow-up period of 17 months. No patients died of ischemic heart disease. Other causes of death included heart

Table 1
Patient characteristics by tertiles of plasma ADPN.

Adiponectin level	Low (n = 184)	Middle (n = 183)	High (n = 181)	p
Age (years)	66 ± 11	71 ± 11	76 ± 10	<0.001
Male (n)	151	124	88	<0.001
Current smoker (n)	64	47	35	0.004
Ischemic heart disease (n)	21	16	25	0.311
Body mass index (kg/m^2)	24.5 ± 3.5	23.4 ± 3.4	21.2 ± 3.5	<0.001
Hypertension	150	140	148	0.366
Diabetes mellitus	60	55	36	0.016
Hyperlipidemia	77	62	52	0.030
Estimated GFR (ml/min/1.73 m^2)	76.2 ± 19.3	75.6 ± 22.8	65.7 ± 27.2	<0.001
Median NIHSS score on admission	5 (range: 0–28)	5 (range: 0–32)	8 (range: 0–36)	0.001
Stroke subtypes (n)				0.004
Atherothrombotic infarction	37	31	21	
Lacunar infarction	35	26	20	
Cardioembolic infarction	28	41	61	
Other types of infarction	43	43	35	
Brain hemorrhage	41	42	44	

Values are mean ± SD; GFR: glomerular filtration rate; NIHSS: National Institutes of Health Stroke scale.

failure (1 patient), cancer (3 patients) and pneumonia (5 patients). Table 2 shows a comparison of cardiovascular risk factors and stroke subtypes between the survivors and the fatal cases. The patients who died were significantly older ($p<0.001$), and had lower body mass index ($p=0.004$), lower diastolic blood pressure ($p=0.040$), lower eGFR ($p=0.021$), and higher plasma ADPN levels ($p<0.001$), higher NIHSS scores on admission ($p<0.001$). In comparison with the stroke subtypes, cardioembolic infarction contained the most fatal cases. There was no significant difference in ADPN levels between those with ischemic stroke and those with brain hemorrhage (11.2 ± 8.4 and 11.8 ± 8.6 μg/ml, respectively).

The survival rates were compared among 3 groups based on tertiles of plasma ADPN levels (Fig. 1). The highest level of ADPN was associated with poor outcome among the 3 groups in both the stroke ($p<0.001$) and all-cause mortalities patients ($p=0.001$).

The results of multivariate Cox regression analyses are shown in Tables 3a and 3b. The highest tertile of ADPN level was a significant predictor of stroke death after adjustment for age and sex (HR: 6.13, 95%CI: 1.61–23.3). Subsequently, with more adjustments for the presence of hypertension, diabetes mellitus, and hyperlipidemia in model 2, the highest tertile of ADPN remained a significant predictor of stroke mortality (HR: 6.55, 95%CI: 1.73–24.8). This association remained significant after additional adjustments for body mass index, eGFR, and NIHSS score on admission in model 3 (HR 4.69, 95% CI: 1.10–20.1). There was no significant interaction between ADPN level and variables for which distribution was different among tertiles of ADPN levels (data not shown). However, the highest tertile of ADPN level was not associated with all-cause mortality.

We analyzed for patients with ischemic stroke ($n=421$) as the same manner as analysis for all patients. The highest tertile of ADPN level was associated with stroke mortality (hazard ratio: 6.90, 95% CI: 1.34–35.5), but not with all-cause mortality (hazard ratio: 1.90, 95% confidence interval: 0.87–4.14) after adjustment for age and sex.

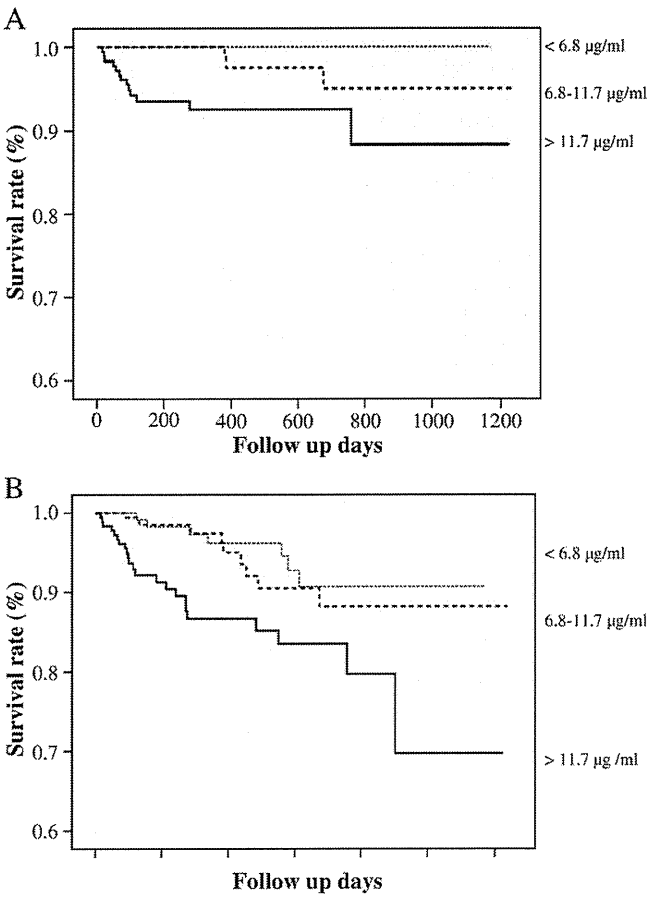

Fig. 1. Kaplan–Meier survival curves according to tertiles of plasma adiponectin concentration for (A) stroke mortality, and (B) all-cause mortality.

Table 2
Comparison of clinical parameters between survivors and fatal cases.

	Survivors (n=509)	Fatalities (n=39)	p
Age (years)	70±11	80±9	<0.001
Male (n)	341	22	0.218
Current smoker (n)	141	5	0.058
Ischemic heart disease (n)	60	2	0.295
Body mass index (kg/m^2)	23.2±3.7	21.4±3.5	0.004
Systolic blood pressure (mm Hg)	134±15	134±15	0.833
Diastolic blood pressure (mm Hg)	72±10	69±9	0.040
Total cholesterol (mg/dl)	170±37	167±36	0.603
Triglycerides (mg/dl)	113±50	102±43	0.167
LDL cholesterol (mg/dl)	108±32	107±37	0.849
HDL cholesterol (mg/dl)	42±12	41±13	0.666
Fasting plasma glucose (mg/dl)	107±35	105±27	0.800
Adiponectin (μg/ml)	10.9±8.1	16.5±10.2	<0.001
Estimated GFR, ml/min/1.73 m^2	73.1±23.5	63.9±26.8	0.021
Median NIHSS score on admission	5 (range: 0–32)	17 (range: 2–36)	<0.001
Stroke subtypes (n)			
Atherothrombotic infarction	85	4	
Lacunar infarction	81	0	
Cardioembolic infarction	111	19	
Other types of infarction			
Undetermined etiology	65	5	
Determined etiology	48	3	
Brain hemorrhage	119	8	

Values are mean±SD; LDL: low-density lipoprotein; HDL: high-density lipoprotein; GFR: glomerular filtration rate; NIHSS: National Institutes of Health Stroke scale.

4. Discussion

This is the first study demonstrating that a high level of plasma ADPN in acute stroke patients was strongly associated with a high risk of stroke death during the median follow-up period of 17 months.

Plasma ADPN levels might change by the influences of stroke severity and stroke subtypes. In this study, there was a significant positive correlation between ADPN levels and NIHSS scores on admission ($r=0.161$, $p<0.001$). Besides, ADPN knock-out mice were shown to exhibit increased cerebral infarction size [5]. Plasma ADPN levels were different in each stroke subtype in this study, consistent with a past study [16]: patients with atherothronbotic brain infarction and lacunar infarction had lower plasma ADPN levels and those with cardioembolic brain infarction had the highest.

ADPN was reported to increase energy expenditure through a direct action in the central nervous system in mice [17]. An increased level of plasma ADPN was observed in patients with heart failure with cachexia [18]. The authors suggested that the increased ADPN, which might occur in an attempt to normalize fatty acid metabolism, would cause body weight loss in patients with advanced heart failure. Recently, high levels of ADPN in patients with CVD were reported to be associated with the increased risk of mortality in both men and women [19,20]. In patients with coronary artery disease, high levels of ADPN turned out to be a risk factor for future CVD events or death [10,21,22], although another report showed no association between high levels of ADPN and CVD death [23]. Marousi S, et al. [24] reported that ADPN was significantly suppressed already by the early phases of ischemic stroke, and remained unchanged 6 months later. Prognostic implications in levels of ADPN have not been clarified. And they

Table 3a
Results of multivariate Cox regression analysis for the incidence of fatal events considering the highest tertile of adiponectin concentration against the middle plus the lowest tertiles.

	Hazard ratio (95% CI)	p
Stroke mortality		
Model 1	6.13 (1.61–23.3)	0.008
Model 2	6.55 (1.73–24.8)	0.006
Model 3	4.69 (1.10–20.1)	0.037
All-cause mortality		
Model 1	1.75 (0.88–3.48)	0.112
Model 2	1.89 (0.95–3.77)	0.070
Model 3	1.19 (0.54–2.62)	0.675

CI: confidence interval.
Model 1: adjusted for age and sex. Model 2 includes the covariates in model 1 plus the presence of hypertension, diabetes mellitus, and hyperlipidemia. Model 3 includes the covariates in model 2 plus body mass index, NIHSS score on admission, and estimated glomerular filtration rate.

recently reported that ADPN was not found to be associated with mortality after the ischemic stroke [25]. But their sample size is very small (n = 82), and follow up period is too short (6 months).

Another possible reason of high mortality in patients with high levels of ADPN could be the low clearance of ADPN attributable to the renal dysfunction. The kidneys are the main elimination apparatus for circulating ADPN [26,27]. Mild renal dysfunction as well as chronic kidney disease was a strong predictor of mortality and poor outcome in both patients with myocardial infarction [28] and stroke [29]. In the present study, eGFR was lower and ADPN was higher in the fatal cases than in the survivors. Relative to this observation, a high level of ADPN was demonstrated to associate with high mortality in patients with chronic kidney disease [11].

The present study was observational, and can only demonstrate associations. We speculate that ADPN plays a protective role in vascular injuries through exerting anti-atherosclerosis or anti-inflammatory effects; however, in high risk patients, such as CVD patients, ADPN level were raised to compensate for vascular injuries, which could result in harmful effects, notably, body weight loss and sarcopenia.

The limitations of this study are that the present investigation was conducted at a single-center with a prospective design. The sample size as well as the follow-up period might not be large enough to have a sufficient statistical power. However we demonstrated a strong association between high ADPN levels and increased risk of stroke mortality. Another limitation is that we measured total ADPN in the present study. It is known that ADPN consists of isoforms with various molecular weights (low-molecular weight; LMW, medium molecular weight; MMW, and high-molecular weight; HMW). These isoforms have different binding affinities for the ADPN receptors, and may have different bioactivities. Recently, a number of reports showed that HMW form of ADPN has more biological activity than LMW or MMW ADPN [30,31]. HMW ADPN, especially the HMW to total ADPN ratio, was significantly lower in patients with coronary artery disease than those without coronary artery disease in patients with type 2 diabetes [31]. Further analysis of ADPN isoforms with respect to cerebrovascular risk factors might clarify the contribution of ADPN to the pathogenesis of cerebrovascular disease.

Table 3b
Hazard ratio of each variable in Cox regression analysis (Model 3).

	Stroke death		All-cause death	
	Hazard ratio	p	Hazard ratio	p
Adiponectin level	4.69 (1.10–20.1)	0.037	1.19 (0.54–2.62)	0.675
Age	1.06 (0.99–1.13)	0.124	1.07 (1.03–1.11)	0.001
Sex	1.38 (0.46–4.16)	0.569	1.07 (0.53–2.16)	0.847
Hypertension	1.81 (0.39–8.32)	0.447	1.82 (0.74–4.46)	0.190
Diabetes mellitus	3.73 (1.10–12.7)	0.035	1.72 (0.78–3.80)	0.183
Hyperlipidemia	0.43 (0.11–1.67)	0.221	0.41 (0.18–0.93)	0.032
Body mass index	0.88 (0.74–1.06)	0.177	0.94 (0.84–1.05)	0.247
NIHSS score on admission	1.08 (1.01–1.16)	0.024	1.11 (1.07–1.16)	<0.001
Estimated GFR	1.01 (0.99–1.03)	0.377	1.00 (0.98–1.01)	0.537

NIHSS: National Institutes of Health Stroke scale; GFR: glomerular filtration rate.

In conclusion, a high level of ADPN in acute stroke patients was associated with an increased risk of stroke death during the 17 months of median follow up period after stroke. Further experimental and epidemiological studies are needed to elucidate possible roles of ADPN in cerebrovascular diseases.

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References

[1] Matsuzawa Y, Funahashi T, Kihara S, Shimomura I. Adiponectin and metabolic syndrome. Arterioscler Thromb Vasc Biol 2004;24:29–33.
[2] Kumada M, Kihara S, Sumitsuji S, Kawamoto T, Matsumoto S, Ouchi N, et al. Association of hypoadiponectinemia with coronary artery disease in men. Arterioscler Thromb Vasc Biol 2003;23:85–9.
[3] Chen MP, Tsai JCR, Chung FM, Yang SS, Hsing LL, Shin SJ, et al. Hypoadiponectinemia is associated with ischemic cerebrovascular disease. Arterioscler Thromb Vasc Biol 2005;25:821–6.
[4] Efstathiou SP, Tsioulos DI, Tsiakou AG, Gratsias YE, Pefanis AV, Mountokalakis TD. Plasma adiponectin levels and five-year survival after first-ever ischemic stroke. Stroke 2005;36:1915–20.
[5] Nishimura M, Izumiya Y, Higuchi A, Shibata R, Qiu J, Kudo C, et al. Adiponectin prevents cerebral ischemic injury through endotherial nitric oxide synthase-dependent mechanisms. Circulation 2008;117:216–23.
[6] Laughlin GA, Barrett-Connor E, May S, Langenberg C. Association of adiponectin with coronary heart disease and mortality: the Rancho Bernardo study. Am J Epidemiol 2007;165:164–74.
[7] Kistorp C, Faber J, Galatius S, Gustafsson F, Frystyk J, Flyvbjerg A, et al. Plasma adiponectin, body mass index, and mortality in patients with chronic heart failure. Circulation 2005;112:1756–62.
[8] George J, Patal S, Wexler D, Sharabi Y, Peleg E, Kamari Y, et al. Circulating adiponectin concentrations in patients with congestive heart failure. Heart 2006;92:1420–4.
[9] Wannamethee SG, Whincup PH, Lennon L, Sattar N. Circulating adiponectin levels and mortality in elderly men with and without cardiovascular disease and heart failure. Arch Intern Med 2007;167:1510–7.
[10] Cavusoglu E, Ruwende C, Chopra V, Yanamadala S, Eng C, Clark LT, et al. Adiponectin is an independent predictor of all-cause mortality, cardiac mortality, and myocardial infarction in patients presenting with chest pain. Eur Heart J 2006;27:2300–9.
[11] Menon V, Li L, Wang X, Greene T, Balakrishnan V, Madero M, et al. Adiponection and mortality in patients with chronic kidney disease. J Am Soc Nephrol 2006;17: 2599–606.
[12] Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MRS, Yen FT, et al. Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad Sci USA 2001;98:2005–10.
[13] Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982–92.
[14] Yokota C, Minematsu K, Hasegawa Y, Yamaguchi T. Long-term prognosis, by stroke subtypes, after a first ever stroke: a hospital-based study over a 20-year period. Cerebrovasc Dis 2004;18:111–6.
[15] Minematsu K, Yamaguchi T, Omae T. 'Spectacular shrinking deficit': rapid recovery from a major hemispheric syndrome by migration of an embolus. Neurology 1992;42:157–62.
[16] Bang OY, Saver JL, Ovbiagele B, Choi YJ, Yoon SR, Lee KH. Adiponectin levels in patients with intracranial atherosclerosis. Neurology 2007;68:1931–7.
[17] Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, et al. Adiponectin acts in the brain to decrease body weight. Nat Med 2004;10:524–9.
[18] McEntegart MB, Awede B, Petie MC, Sttar N, Dunn FG, MacFarlane NG, et al. Increase in serum adiponectin concentration in patients with heart failure and cachexia: relationship with leptin, other cytokines, and B-type natriuretic peptide. Eur Heart J 2007;28:829–35.

[19] Dekker JM, Funahashi T, Nijpels G, Pilz S, Stehouwer CDA, Snijder MB, et al. Prognostic value of adiponectin for cardiovascular disease and mortality. J Clin Endocrinol Metab 2008;93:1489–96.
[20] Kizer JR, Barzilay JI, Kuller LH, Gottdiener JS. Adiponectin and risk of coronary heart disease in older men and women. J Clin Endocrinol Metab 2008;93:3357–64.
[21] Pilz S, Mangge H, Wellnitz B, Seelhorst U, Winkelmann BR, Tiran B, et al. Adiponectin and mortality in patients undergoing coronary angiography. J Clin Endocrinol Metab 2006;91:4277–86.
[22] Schnabel R, Messow CM, Lubos E, Espinola-Klein C, Rupprecht HJ, Bickel C, et al. Association of adiponectin with adverse outcome in coronary artery disease: results from the AtheroGene study. Eur Heart J 2008;29:649–57.
[23] Maiolino G, Cesari M, Sticchi D, Zanchetta M, Pedon L, Antezza K, et al. Plasma adiponectin for prediction of cardiovascular events and mortality in high-risk patients. J Clin Endocrinol Metab 2008;93:3333–40.
[24] Marousi S, Theodorou G, Karakantza M, Papathanasopoulos P, Ellul J. Serum adiponectin acutely after an ischemic stroke: implications for long-lasting, suppressed anti-inflammatrory role. Acta Neurol Scand 2010;121:277–84.
[25] Marousi SG, Theodorou GL, Karakantza M, Zampakis P, Papathanasopoulos P, Ellul J. Acute post-stroke adiponectin in relation to stroke severity, progression and 6 month functional outcome. Neurol Res 2010;32:841–4.
[26] Koshimura J, Fujita H, Narita T, Shimotomai T, Hosoba M, Yoshioka N, et al. Urinary adiponectin excretion is increased in patients with overt diabetic nephropathy. Biochem Biophys Res Commun 2004;316:165–9.
[27] Wakabayashi S, Aso Y. Adiponectin concentrations in sera from patients with type 2 diabetes are negatively associated with sympathovagal balance as evaluated by power spectral analysis of heart rate variation. Diab Care 2004;27:2392–7.
[28] Anavekar NS, McMurray JJV, Velazquez EJ, Solomon SD, Kober L, Rouleau JL, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285–95.
[29] Yahalom G, Schwartz R, Schwammenthal Y, Merzeliak O, Toashi Maya, Orion D, et al. Chronic kidney disease and clinical outcome in patients with acute stroke. Stroke 2009;40:1296–303.
[30] Lara-Castro C, Luo N, Wallace P, Klein RL, Garvey WT. Adiponectin multimeric complexes and the metabolic syndrome trait cluster. Diabetes 2006;55:249–59.
[31] Aso Y, Yamamoto R, Wakabayashi S, Uchida T, Takayanagi K, Takebayashi K, et al. Comparison of serum high-molecular weight (HMW) adiponectin with total adiponectin concentrations in type 2 diabetic patients with coronary artery disease using a novel enzyme-linked immunosorbent assay to detect HMW adiponectin. Diabetes 2006;55:1954–60.

Early Ischemic Change on CT Versus Diffusion-Weighted Imaging for Patients With Stroke Receiving Intravenous Recombinant Tissue-Type Plasminogen Activator Therapy

Stroke Acute Management With Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry

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Background and Purpose—Alberta Stroke Programme Early CT Score (ASPECTS) is a quantitative topographical score to evaluate early ischemic change in the middle cerebral arterial territory on CT as well as on diffusion-weighted imaging (DWI). The aim of the present study was to elucidate the relationship between CT-ASPECTS and DWI-ASPECTS for patients with hyperacute stroke and their associations with outcomes after recombinant tissue-type plasminogen activator therapy based on a multicenter registry.

Methods—ASPECTS was assessed on both CT and DWI before intravenous 0.6 mg/kg alteplase in 360 patients with stroke (119 women, 71±11 years old). The outcomes were symptomatic intracerebral hemorrhage within 36 hours and independence at 3 months defined by a modified Rankin Scale score of 0 to 2.

Results—DWI-ASPECTS was positively correlated with CT-ASPECTS (ρ=0.511, P<0.001) and was lower than CT-ASPECTS (median 8 [interquartile range, 6 to 9] versus 9 [8 to 10], P<0.001). Higher baseline National Institutes of Health Stroke Scale score (standardized partial regression coefficient [β] 0.061, P<0.001) and cardioembolic stroke (β 0.35, P<0.001) were related to this discrepancy. The area under the receiver operating characteristic curve for predicting sICH (12 patients) using ASPECTS was 0.673 (95% CI, 0.503 to 0.807) by CT and 0.764 (95% CI, 0.635 to 0.858) by DWI (P=0.275). The area for predicting independence at 3 months (192 patients) was 0.621 (0.564 to 0.674) by CT and 0.639 (0.580 to 0.694) by DWI (P=0.535).

Conclusions—For patients with hyperacute stroke, DWI-ASPECTS scored approximately 1 point lower than CT-ASPECTS. Both CT-ASPECTS and DWI-ASPECTS were useful predictors of symptomatic intracerebral hemorrhage and independence at 3 months after recombinant tissue-type plasminogen activator. (***Stroke.* 2011;42:2196-2200.)**

Key Words: acute stroke ■ diffusion-weighted MRI ■ early ischemic sign ■ thrombolysis

Early ischemic change (EIC) of the brain is predictive of the benefit from thrombolysis.[1–3] EIC on CT has been assessed by using the one third of cerebral hemisphere rule, and patients with extensive EIC are contraindicated for administration of intravenous recombinant tissue-type plasminogen activator (rtPA) within 3 to 4.5 hours of onset of acute ischemic stroke.[4–6] The Alberta Stroke Programme Early CT Score (ASPECTS) was successfully developed to improve reliability for the detection of EIC on CT imaging.[7] However, EIC on CT is subtle and has poor intra- and interrater reliabilities.[8]

MRI with diffusion-weighted imaging (DWI) is better than CT for detection of acute ischemic stroke. MRI could be used as the first-line modality for the emergent imaging of patients with acute stroke.[9,10] ASPECTS has been recently applied to

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assess EIC on DWI.[11,12] We reported that pretreatment ASPECTS on DWI was independently predictive of functional and vital outcomes at 3 months after rtPA therapy from single-center and multicenter registries.[13,14] To our knowledge, EIC on CT has been compared with that on MRI before rtPA therapy using ASPECTS only in a few studies[15,16]; 1 small study, involving 22 patients with stroke, reported that ASPECTS on DWI seemed to be useful for predicting neurological deterioration after thrombolysis.[16] The aim of the present study was to elucidate the relationship between pretreatment ASPECTS assessed using CT and DWI before rtPA therapy and their associations with outcomes after stroke.

Subjects and Methods

The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rtPA Registry was conducted using a multicenter hospital-based retrospective observational design. The details of this study have been described previously.[14,17] In brief, a total of 600 consecutive patients with acute ischemic stroke receiving intravenous rtPA were registered from October 2005 (when intravenous alteplase therapy was approved in Japan) through July 2008 in 10 stroke centers in Japan. Patient eligibility for alteplase therapy was determined based on the Japanese guideline for intravenous rtPA therapy, which followed the inclusion and exclusion criteria used in the National Institute of Neurological Disorders and Stroke study and the Japan Alteplase Clinical Trial (J-ACT).[18,19] According to the Japanese guidelines,[20] patients with CT-documented extensive EIC (size is not defined) were not eligible for the treatment. Because the guidelines do not refer to EIC on DWI, the eligibility of patients having large EIC on DWI depended on each physician's decision. Each local ethics committee approved the retrospective collection of clinical data from the database and submission of the data to our central office. Each patient received a single alteplase dose of 0.6 mg/kg (the recommended dose in Japanese guidelines and the approved labeling) intravenously with 10% given as a bolus within 3 hours of stroke onset followed by a continuous intravenous infusion of the remainder over 1 hour.

Baseline data, including sex, age, comorbidities (hypertension, diabetes, hyperlipidemia, and congestive heart failure), blood pressure on admission, time from onset to treatment, neurological deficits using the National Institutes of Health Stroke Scale score, and stroke subtype according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) categories,[21] were collected retrospectively from medical charts for all patients.

Assessment of ASPECTS on CT and DWI

Before rtPA infusion, MRI studies, including DWI and MR angiography, were begun principally after CT. Time of starting CT and MRI were collected from medical charts. Administration of rtPA was begun approximately 10 minutes after MRI. CT scans were performed in almost all centers according to a standard CT scan protocol (5- to 10-mm slice thickness without contrast enhancement, 120 kV, high tube current, low speed scan with ≥2 seconds/rotation, contrast-favored algorithm, inferior orbitomeatal baseline, filmed at appropriate window width of ≥80 Hounsfield units). MRI scans were performed on a 1.5-T scanner. MRI protocols were not entirely uniform in each center, but all included an axial DWI using a single-shot echoplanar imaging (b=1000 s/mm^2, 5- to 6-mm-thick slices). The time required to perform CT was a few minutes and that of MRI was 10 to 15 minutes. ASPECTS assessed using DWI (DWI-ASPECTS) as well as original ASPECTS based on CT (CT-ASPECTS) was examined by each investigator in each center without using a central reading system. Thus, the reading results reflect real-life conditions. At least 2 experienced vascular neurologists or neurosurgeons in each stroke center evaluated the initial DWI and CT images to calculate quantitative EIC using ASPECTS later as a post hoc analysis. The interrater agreement of ASPECTS in our study group assessed using a sample of 76 CT and DWI images was ρ=0.634 for CT (P<0.001) and ρ=0.818 for DWI (P<0.001, Spearman rank test). Arterial occlusion was (principally) assessed on the initial MR angiography.

Table 1. Baseline Characteristics

	n=360
Women	119 (33.1)
Age, y	71±11
Hypertension	215 (60.2)
Diabetes mellitus	63 (17.6)
Dyslipidemia	71 (19.8)
Congestive heart failure	20 (5.7)
Pretreatment systolic blood pressure, mm Hg	151±21
Pretreatment diastolic blood pressure, mm Hg	82±15
Baseline NIHSS	12 (7–18)
CT-ASPECTS	9 (8–10)
DWI-ASPECTS	8 (6–9)
Arterial occlusion site	
Internal carotid artery	58 (16.1)
Middle cerebral artery trunk (M1)	119 (33.1)
Middle cerebral artery branch (M2 or M3)	81 (22.5)
Not occluded*	102 (28.3)
Stroke subtype	
Cardioembolism	217 (60.3)
Atherothrombotic stroke	52 (14.4)
Lacune	21 (5.8)
Other	70 (19.5)
Onset to treatment time, min	140 (120–165)
Time delay of MRI after CT, min (n=323)	19 (12–29)

Data are no. of patients (%), median (interquartile range) for discontinuous variables, and mean±SD for continuous variables.

NIHSS indicates National Institutes of Health Stroke Scale score; ASPECTS, Alberta Stroke Programme Early CT Score; DWI, diffusion-weighted imaging; MRI, magnetic resonance imaging; CT, computed tomography; M1, middle cerebral artery trunk (horizonal segment); M2, middle cerebral artery branch (sylvian segment); M3, middle cerebral artery branch (cortical segment).

*Including patients who have insufficient-quality MR angiography.

Outcomes

The outcomes were symptomatic intracerebral hemorrhage (sICH) within the initial 36 hours and independence at 3 months corresponding to a modified Rankin Scale score of 0 to 2. Intracerebral hemorrhage was defined as CT evidence of new parenchymal hemorrhage of Type I or Type II within the initial 36 hours[2] and was assessed by at least 2 experienced examiners. sICH was defined as a parenchymal intracerebral hemorrhage associated with neurological deterioration corresponding to an increase of ≥4 points from the baseline National Institutes of Health Stroke Scale score.

Statistical Analysis

Statistical analysis was performed using the JMP 8.0 statistical software (SAS Institute Inc, Cary, NC). The relationship between CT-ASPECTS and DWI-ASPECTS was assessed by Spearman rank test, the Bland and Altman plot, and an interrater correlation coefficient. Multiple linear regression was performed to identify the predictors for the discrepancy between CT-ASPECTS and DWI-ASPECTS based on the characteristics in Table 1. CT-ASPECTS and DWI-ASPECTS in patients with middle cerebral artery occlusion were compared with those in patients without by the Mann–Whitney U test. Sensitivity and specificity of EIC on each region of

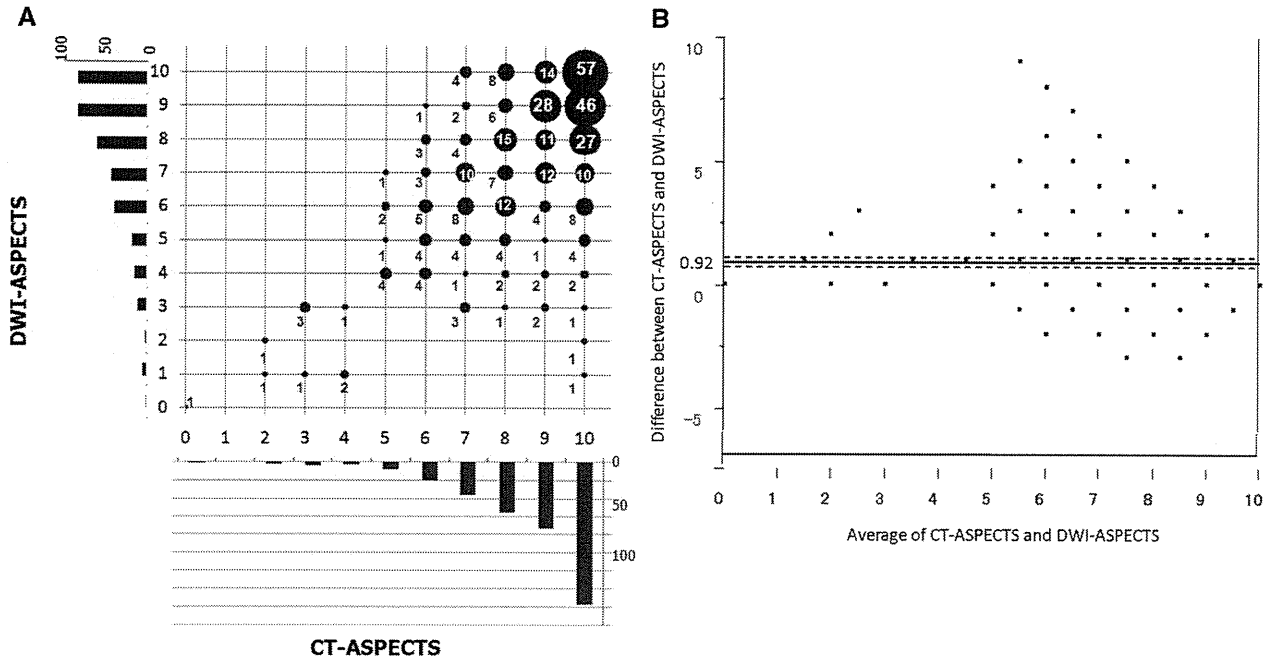

Figure 1. Number of patients assessed using CT-ASPECTS and DWI-ASPECTS (**A**). Bland and Altman plot of CT-ASPECTS and DWI-ASPECTS. The mean difference between CT-ASPECTS and DWI-ASPECTS was +0.92. The horizontal line showed the mean difference in scores and the dotted lines showed the 95% CI (**B**). ASPECTS indicates Alberta Stroke Programme Early CT Score; DWI, diffusion-weighted imaging; CT, computed tomography.

CT-ASPECTS were assessed when setting DWI-ASPECTS as a standard. To evaluate the predictive ability of the CT-ASPECTS and DWI-ASPECTS for each outcome, receiver operating characteristic curves were constructed. The area under the receiver operating characteristic curve was used as a scalar measure to assess the performance of prognostic risk scores. The comparison of area under the receiver operating characteristic curves was conducted by nonparametric method.[22] Statistical significance was established at $P<0.05$.

Results

Of the total of 600 consecutive patients registered, the following 240 patients were deemed ineligible for the study: 109 patients who had a history of ischemic stroke; 20 who had premorbid modified Rankin Scale scores of 3 to 5; 58 who were not performed MRI due to contraindications, unsteadiness, or time limitation; 6 who had CT or DWI images of insufficient quality to evaluate EIC; 43 who had vertebrobasilar, posterior cerebral arterial, or anterior cerebral arterial territory strokes; and 3 who had missing data on 3-month modified Rankin Scale scores. Finally, 360 patients (241 men, 71±11 years old) were included in the study. Baseline clinical characteristics of the patients are presented in Table 1. The median National Institutes of Health Stroke Scale score was 12 (interquartile range, 7 to 18). Time delay between CT and MRI was identified in 323 patients (89.7%); the median delay was 19 minutes (interquartile range, 12 to 29).

The pretreatment DWI-ASPECTS was positively correlated with CT-ASPECTS ($\rho=0.511$, $P<0.001$, Spearman rank test; Figure 1A). An interrater correlation coefficient between CT-ASPECTS and DWI-ASPECTS was 0.535. DWI-ASPECTS (median, 8; interquartile range, 6 to 9) was lower than CT-ASPECTS (9; 8 to 10; $P<0.001$). Figure 1B shows the Bland and Altman plot. The mean difference between CT-ASPECTS and DWI-ASPECTS was 0.92 (95% CI, 0.74 to 1.10). On multiple linear regression analysis, baseline National Institutes of Health Stroke Scale (standardized partial regression coefficient [β] 0.061, $P<0.001$) and cardioembolism (β 0.35, $P<0.001$) were related to the discrepancy between CT-ASPECTS and DWI-ASPECTS. CT-ASPECTS was ≥8 in 286 patients (79.4%); of these, 21 patients (7.3%) had DWI-ASPECTS of ≤5. Of these 21 patients, 2 patients had sICH. CT-ASPECTS and DWI-ASPECTS (median, 9; interquartile range, 7 to 10 and 8; 6 to 9, respectively) in patients with middle cerebral artery occlusion were lower than those in patients without (median, 10; interquartile range, 9 to 10 and 9; 9 to 10, respectively; $P<0.001$ for both).

The sensitivity and specificity of EIC on each region of CT-ASPECTS when using DWI-ASPECTS as the gold standard are shown in Table 2. The sensitivities of EICs in the caudate and internal capsule regions (13.0% and 18.0%, respectively) and the specificity of EIC in the lentiform nucleus (86.2%) were relatively low on CT.

Of 360 patients, 76 (21.1%) had any intracerebral hemorrhage, 12 (3.3%) had sICH, and 192 (53.3%) were independent (modified Rankin Scale 0 to 2). For prediction of sICH, the area under the receiver operating characteristic curve was 0.673 (95% CI, 0.503 to 0.807) for CT-ASPECTS and 0.764 (0.635 to 0.858) for DWI-ASPECTS ($P=0.275$; Figure 2A). For prediction of independence at 3 months, the area under the receiver operating characteristic curve was 0.621 (0.564 to 0.674) for CT-ASPECTS and 0.639 (0.580 to 0.694) for DWI-ASPECTS ($P=0.535$; Figure 2B).

Discussion

In this study, DWI-ASPECTS was positively related with CT-ASPECTS, scored lower than CT-ASPECTS, and was as

Table 2. Sensitivity and Specificity of Early Ischemic Change on Each Region of ASPECTS

	Frequency of EIC, %				
	CT	DWI	Both	Sensitivity, %	Specificity, %
Caudate (C)	2.2	12.8	1.7	13.0	99.4
Lentiform nucleus (L)	22.2	27.8	12.2	44.0	86.2
Internal capsule (IC)	5.0	13.9	2.5	18.0	97.1
Insular ribbon (I)	32.5	45.3	25.8	57.1	87.8
M1	11.4	21.7	9.7	44.9	97.8
M2	19.7	26.1	13.3	51.1	91.4
M3	8.9	15.6	6.1	39.3	96.7
M4	7.2	14.2	5.3	37.3	97.7
M5	17.5	31.1	12.5	40.2	92.7
M6	7.8	18.6	6.4	34.3	98.3

ASPECTS indicates Alberta Stroke Programme Early CT Score; DWI, diffusion-weighted imaging; CT, computed tomography; EIC, early ischemic change; M1, anterior MCA (middle cerebral artery) cortex; M2, MCA cortex lateral to insular ribbon; M3, posterior MCA cortex; M4, M5, and M6 are anterior, lateral, and posterior MCA territories, respectively, approximately 2 cm superior to M1, M2, and M3, respectively, rostral to basal ganglia.

useful as CT-ASPECTS for predicting functional outcomes in patients with hyperacute stroke who were scheduled to receive rtPA therapy. We elucidated the relationship between DWI-ASPECTS and CT-ASPECTS before rtPA therapy and their associations with outcomes after therapy. We followed much a previous study design by Barber et al[15] involving 100 patients within 6 hours of stroke onset. The strength of our study compared with the previous 1 was the larger sample size, shorter time interval between stroke onset and imaging examination, and shorter time interval between CT and DWI.

This study demonstrates that DWI-ASPECTS scored approximately 1 point lower than CT-ASPECTS in patients with stroke within 3 hours of onset. Previously, the reported difference of ASPECTS in both methods was 0.43 on average based on the previously mentioned study by Barber et al[15] and 1 when using the median based on another study involving 30 patients within 24 hours of stroke onset.[23] The time delay of MRI after CT, 102 minutes on average in the former study and 4.4 hours when using the median in the latter study, was proposed as a major reason for the discrepancy in ASPECTS.[15,23] Because the time delay was much smaller in the present study, the discrepancy in ASPECTS appears to be mainly due to the superior ability of DWI to delineate the extension of EIC as compared with CT.

The multivariate analysis indicated that when stroke subtype was cardioembolic and when the initial neurological deficits were severe, CT had the tendency to underestimate extension of EIC than DWI. The time delay of MRI after CT was not related to this discrepancy. Among regions of interest, the sensitivities of EICs in the caudate and internal capsule regions and the specificity of EIC in the lentiform nucleus were low on CT as compared with DWI. Thus, ASPECTS in the 2 modalities may not coincide, particularly in patients with severe cardioembolic stroke whose EICs lie extensively in the basal ganglia. CT seems to have a limitation for delineation of attenuation changes in the caudate and internal capsule regions as compared with that of sulcal effacement, focal cortical swelling, and loss of gray–white differentiation in the cortex because of the low sensitivity. The probable reason for the low specificity in the lentiform in the basal ganglia may be reversed discrepancy between CT and DWI.[24] Reversed discrepancy was identified mainly in the basal ganglia, and its pathophysiology may be pseudonormalization of apparent diffusion coefficient in EIC by early spontaneous reperfusion.[24] A critical limitation in our Table 2 was that the analysis was referenced to DWI, which incorporates both reversible and irreversible ischemia. The analysis should be fundamentally referenced to follow-up imaging, which represents final tissue status. However, our patients were treated with rtPA and natural courses of final tissue status could not be assessed.

Another unique finding in this study was comparison of CT-ASPECTS and DWI-ASPECTS as an outcome predictor. The area under the receiver operating characteristic curves for predicting outcomes with DWI-ASPECTS were somewhat,

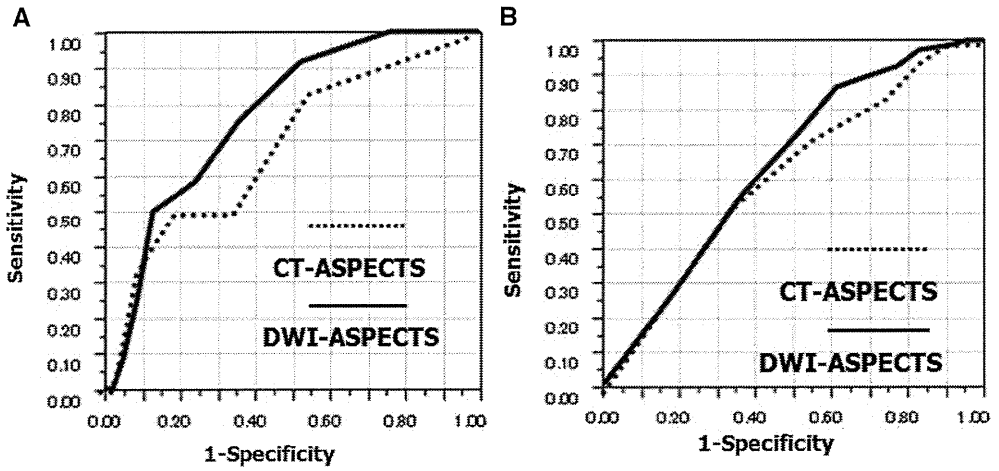

Figure 2. Receiver operating characteristic (ROC) curves of ASPECTS (CT or DWI) for predicting symptomatic intracerebral hemorrhage (**A**). ROC curves of ASPECTS (CT or DWI) for predicting modified Rankin Scale scores of 0 to 2 (**B**). ASPECTS indicates Alberta Stroke Programme Early CT Score; DWI, diffusion-weighted imaging; CT, computed tomography.

although not significantly, higher than those with CT-ASPECTS. DWI-ASPECTS appears to be at least equivalent to CT-ASPECTS in predicting sICH and stroke outcomes.

This study has several limitations. First, this was an observational study and patient eligibility for rtPA was determined according to each patient's situation, although the determination was principally based on the Japanese guidelines.[20] These guidelines might have contributed to selection bias. Second, all the patients were treated with 0.6 mg/kg alteplase. Thus, the clinical values of CT-ASPECTS and DWI-ASPECTS in patients treated with 0.9 mg/kg alteplase were not ascertained. Third, although we tried to perform CT and MRI as quickly as possible, onset to treatment time might have been somewhat longer than if only 1 of the examinations had been done. Finally, the present analysis was done only for patients without extensive EIC; this selection bias affects statistical results.

Our findings support the use of DWI-ASPECTS as well as CT-ASPECTS in predicting clinical outcomes after rtPA therapy. In addition, DWI-ASPECTS in our cohorts showed higher interrater reliability as compared with CT-ASPECTS as was reported in previous reports.[25,26] DWI-ASPECTS is a promising scoring system to evaluate EIC for predicting reliable clinical outcomes in future clinical stroke trials.

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References

1. Moulin T, Cattin F, Crepin-Leblond T, Tatu L, Chavot D, Piotin M, et al. Early CT signs in acute middle cerebral artery infarction: predictive value for subsequent infarct locations and outcome. *Neurology*. 1996;47:366–375.
2. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995;274:1017–1025.
3. Silver B, Demaerschalk B, Merino JG, Wong E, Tamayo A, Devasenapathy A, et al. Improved outcomes in stroke thrombolysis with pre-specified imaging criteria. *Can J Neurol Sci*. 2001;28:113–119.
4. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke*. 2007;38:1655–1711.
5. Norris JW, Buchan A, Cote R, Hachinski V, Phillips SJ, Shuaib A, et al. Canadian guidelines for intravenous thrombolytic treatment in acute stroke. A consensus statement of the Canadian Stroke Consortium. *Can J Neurol Sci*. 1998;25:257–259.
6. The European Stroke Organisation Executive Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457–507.
7. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. *Lancet*. 2000;355:1670–1674.
8. Wardlaw JM, Mielke O. Early signs of brain infarction at CT: observer reliability and outcome after thrombolytic treatment—systematic review. *Radiology*. 2005;235:444–453.
9. Kang DW, Chalela JA, Dunn W, Warach S. MRI screening before standard tissue plasminogen activator therapy is feasible and safe. *Stroke*. 2005;36:1939–1943.
10. Schellinger PD, Thomalla G, Fiehler J, Kohrmann M, Molina CA, Neumann-Haefelin T, et al. MRI-based and CT-based thrombolytic therapy in acute stroke within and beyond established time windows: an analysis of 1210 patients. *Stroke*. 2007;38:2640–2645.
11. Singer OC, Kurre W, Humpich MC, Lorenz MW, Kastrup A, Liebeskind DS, et al. Risk assessment of symptomatic intracerebral hemorrhage after thrombolysis using DWI-ASPECTS. *Stroke*. 2009;40:2743–2748.
12. Kimura K, Iguchi Y, Shibazaki K, Terasawa Y, Inoue T, Uemura J, et al. Large ischemic lesions on diffusion-weighted imaging done before intravenous tissue plasminogen activator thrombolysis predicts a poor outcome in patients with acute stroke. *Stroke*. 2008;39:2388–2391.
13. Nakashima T, Toyoda K, Koga M, Matsuoka H, Nagatsuka K, Takada T, et al. Arterial occlusion sites on magnetic resonance angiography influence the efficacy of intravenous low-dose (0.6 mg/kg) alteplase therapy for ischaemic stroke. *Int J Stroke*. 2009;4:425–431.
14. Nezu T, Koga M, Kimura K, Shiokawa Y, Nakagawara J, Furui E, et al. Pretreatment ASPECTS on DWI predicts 3-month outcome following rt-PA: SAMURAI rt-PA Registry. *Neurology*. 2010;75:555–561.
15. Barber PA, Hill MD, Eliasziw M, Demchuk AM, Pexman JH, Hudon ME, et al. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *J Neurol Neurosurg Psychiatry*. 2005;76:1528–1533.
16. Morita N, Harada M, Uno M, Matsubara S, Nagahiro S, Nishitani H. Evaluation of initial diffusion-weighted image findings in acute stroke patients using a semiquantitative score. *Magn Reson Med Sci*. 2009;8:47–53.
17. Toyoda K, Koga M, Naganuma M, Shiokawa Y, Nakagawara J, Furui E, et al. Routine use of intravenous low-dose recombinant tissue plasminogen activator in Japanese patients. General outcomes and prognostic factors from the SAMURAI Register. *Stroke*. 2009;40:3591–3595.
18. The National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.
19. Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, et al. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan Alteplase Clinical Trial (J-ACT). *Stroke*. 2006;37:1810–1815.
20. Shinohara Y, Yamaguchi T. Outline of the Japanese guidelines for the management of stroke 2004 and subsequent revision. *Int J Stroke*. 2008;3:55–62.
21. Adams HP Jr, Bendixen BH, Kappelle LJ, 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.
22. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44:837–845.
23. Kosior RK, Lauzon ML, Steffenhagen N, Kosior JC, Demchuk A, Frayne R. Atlas-based topographical scoring for magnetic resonance imaging of acute stroke. *Stroke*. 2010;41:455–460.
24. Kim EY, Ryoo JW, Roh HG, Lee KH, Kim SS, Song IC, et al. Reversed discrepancy between CT and diffusion-weighted MR imaging in acute ischemic stroke. *AJNR Am J Neuroradiol*. 2006;27:1990–1995.
25. Saur D, Kucinski T, Grzyska U, Eckert B, Eggers C, Niesen W, et al. Sensitivity and interrater agreement of CT and diffusion-weighted MR imaging in hyperacute stroke. *AJNR Am J Neuroradiol*. 2003;24:878–885.
26. Barber PA, Darby DG, Desmond PM, Gerraty RP, Yang Q, Li T, et al. Identification of major ischemic change. Diffusion-weighted imaging versus computed tomography. *Stroke*. 1999;30:2059–2065.