After multivariate adjustment, any ICH was less common in patients in the OUT group than those in the IN group, but the frequency of symptomatic ICH did not differ significantly between the groups. Unfavorable outcome and death were more common in the OUT group than in the IN group and in patients with a NIHSS score ≥25 compared with those <25. Unfavorable outcome was also more common in patients >80 years than those ≤80 years (Table). The Figure shows the distribution of patients and their modified Rankin Scale scores at 3 months.

Discussion

More than 25% of ischemic strokes occur in patients ≥80 years old in Japan.[4] Advanced age was reported to be a strong predictor of poor outcomes and mortality independent of other clinical characteristics.[5] Randomized trials on rtPA did not include a sufficient number of patients with advanced age.[6–9] In the National Institute of Neurological Disorders and Stroke trial,[6] rtPA treatment was associated with increased likelihood of favorable outcome 3 months after stroke even in 49 patients aged >75 years with a NIHSS score >20 as compared with the placebo group. Risk of symptomatic ICH after thrombolysis did not increase, although clinical outcomes were worse in patients >80 years old as compared with younger patients in several studies.[10–13] An adjusted, controlled comparison based on 3472 patients >80 years old showed a better distribution of the modified Rankin Scale in thrombolysis patients than nonthrombolysis patients.[14] In this study, 0.6 mg/kg of alteplase may have caused the relatively small number of symptomatic ICH both in patients older than and ≤80 years old.

Diabetes mellitus was independently associated with symptomatic ICH after standard-dose rtPA therapy.[15] Infrequent development of ICH in our cohort and exclusion of patients with premorbid modified Rankin Scale ≥2 from the outcome analysis might weaken the impact of prior stroke plus diabetes on outcomes in this study. The small number of patients with prior stroke plus diabetes might also affect the statistical power.

This was not a randomized controlled study, subgroups were small, and physicians used judgment in selecting patients, all of which limit this study and introduce potential for error. In addition, data for patients with stroke who did not undergo thrombolysis were not collected and a comparison of patients with and without thrombolysis was not done.

In conclusion, 3-month outcomes after low-dose rtPA in patients outside the European indications were less favorable compared with those included in the indications. Low-dose intravenous rtPA therapy may be safely administered to patients outside the European indications without an increase of ICH by careful selection of patients. Patients with prior stroke and concomitant diabetes seem to be appropriate candidates for rtPA therapy.

Sources of Funding

This study was supported in part by Grants-in-Aid (H20-Junkanki-Ippan-019, H23-Junkanki-Ippan-010) from the Ministry of Health, Labor, and Welfare, Japan (MHLW-Japan) and a Grant from the Japan Cardiovascular Research Foundation (Bayer Scholarship for Cardiovascular Research).

Disclosures

M.K. receives grant support from the Japan Cardiovascular Research Foundation. K.M. receives support from Astellas Pharma Inc, Takeda Pharmaceutical Company Limited, Sanofi-Aventis, Lundbeck Inc, Mitsubishi-Tanabe Pharma Corporation, Kyowa-Hakko-Kirin Pharma Inc, Hitachi Medical Corporation, Research Grants for Cardiovascular Diseases and Grants-in-Aid from MHLW-Japan, and the Foundation for Biomedical Research and Innovation. K.T. receives support from Grants-in-Aid, MHLW-Japan.

References

1. Toni D, Lorenzano S, Puca E, Prencipe M. The SITS-MOST registry. *Neurol Sci.* 2006;27(suppl 3):S260–S262.
2. 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.
3. 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.
4. Maeda K, Toyoda K, Minematsu K, Kobayashi S. Sex and age differences in stroke features and outcomes in 33 953 patients: the Japan Standard Stroke Registry Study [Abstract]. *Stroke.* 2010;41:e364.
5. Kammersgaard LP, Jorgensen HS, Reith J, Nakayama H, Pedersen PM, Olsen TS. Short- and long-term prognosis for very old stroke patients. The Copenhagen Stroke Study. *Age Ageing.* 2004;33:149–154.
6. The NINDS tPA Stroke Study Group. Generalized efficacy of tPA for acute stroke. Subgroup analysis of the NINDS tPA Stroke Trial. *Stroke.* 1997;28:2119–2125.
7. 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.
8. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet.* 1998;352:1245–1251.
9. Albers GW, Clark WM, Madden KP, Hamilton SA. ATLANTIS trial: results for patients treated within 3 hours of stroke onset. *Stroke.* 2002; 33:493–495.
10. Tanne D, Gorman MJ, Bates VE, Kasner SE, Scott P, Verro P, et al. Intravenous tissue plasminogen activator for acute ischemic stroke in patients aged 80 years and older: the tPA stroke survey experience. *Stroke.* 2000;31:370–375.
11. Berrouschot J, Rother J, Glahn J, Kucinski T, Fiehler J, Thomalla G. Outcome and severe hemorrhagic complications of intravenous thrombolysis with tissue plasminogen activator in very old (> or =80 years) stroke patients. *Stroke.* 2005;36:2421–2425.
12. Sylaja PN, Cote R, Buchan AM, Hill MD. Thrombolysis in patients older than 80 years with acute ischaemic stroke: Canadian Alteplase for Stroke Effectiveness Study. *J Neurol Neurosurg Psychiatry.* 2006;77:826–829.
13. Ford GA, Ahmed N, Azevedo E, Grond M, Larrue V, Lindsberg PJ, et al. Intravenous alteplase for stroke in those older than 80 years old. *Stroke.* 2010;41:2568–2574.
14. Mishra NK, Ahmed N, Andersen G, Egido JA, Lindsberg PJ, Ringleb PA, et al. Thrombolysis in very elderly people: controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive. *BMJ.* 2010;341:c6046.
15. Demchuk AM, Morgenstern LB, Krieger DW, Linda Chi T, Hu W, Wein TH, et al. Serum glucose level and diabetes predict tissue plasminogen activator-related intracerebral hemorrhage in acute ischemic stroke. *Stroke.* 1999;30:34–39.

Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2012;33:240–247
DOI: 10.1159/000334664

Received: May 6, 2011
Accepted: October 20, 2011
Published online: January 19, 2012

Effect of Serum Lipid Levels on Stroke Outcome after rt-PA Therapy: SAMURAI rt-PA Registry

Noriko Makihara[a] Yasushi Okada[a] Masatoshi Koga[b] Yoshiaki Shiokawa[d] Jyoji Nakagawara[e] Eisuke Furui[f] Kazumi Kimura[g] Hiroshi Yamagami[h] Yasuhiro Hasegawa[i] Kazuomi Kario[j] Satoshi Okuda[k] Masaki Naganuma[c] Kazunori Toyoda[c]

[a]Department of Cerebrovascular Medicine, Cerebrovascular Center and Clinical Research Center, National Hospital Organization Kyushu Medical Center, Fukuoka, [b]Division of Stroke Care Unit and [c]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Osaka, [d]Department of Neurosurgery and Stroke Center, Kyorin University School of Medicine, Mitaka, [e]Department of Neurosurgery and Stroke Center, Nakamura Memorial Hospital, Sapporo, [f]Department of Stroke Neurology, Kohnan Hospital, Sendai, [g]Department of Stroke Medicine, Kawasaki Medical School, Kurashiki, [h]Department of Neurology, Stroke Center, Kobe City General Hospital, Kobe, [i]Department of Neurology, St. Marianna University School of Medicine, Kawasaki, [j]Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Shimotsuke, and [k]Department of Neurology, National Hospital Organization Nagoya Medical Center, Nagoya, Japan

Key Words

Acute stroke · Brain infarction · Dyslipidemia · High-density lipoprotein cholesterol · Statins · Thrombolysis

Abstract

Background: The effects of lipid levels on clinical outcomes after ischemic stroke are controversial. Whether admission lipid levels and prior statin use are associated with early intracerebral hemorrhage (ICH) and long-term functional outcome after recombinant tissue plasminogen activator (rt-PA) therapy for stroke patients was investigated. ***Methods:*** Ischemic stroke patients who received intravenous rt-PA from a multicenter registry were studied. Lipid levels on admission, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, and triglyceride levels, as well as prior statin use, were assessed. The primary outcome was favorable outcome at 3 months corresponding to a modified Rankin Scale score ≤1. The secondary outcome was any or symptomatic ICH within the initial 36 h. ***Results:*** Of 489 enrolled patients (171 women, 70.8 ± 11.6 years old), 60 used statins prior to stroke, 93 developed ICH (19.0%), and 188 (38.4%) had a favorable 3-month outcome. Of the lipid levels, only the HDL-C level was an independent predictor of favorable outcome after multivariate adjustment for baseline characteristics (OR 1.95, 95% CI 1.10–3.47 per 1 mmol/l; p = 0.023) and after further adjustment for pretreatment radiological findings (OR 2.03, 95% CI 1.07–3.84; p = 0.029). For the 187 stroke patients without cardioembolism, the HDL-C level was more strongly associated with favorable outcome (OR 4.94, 95% CI 1.91–12.76 per 1 mmol/l; p = 0.001). There were no significant associations between ICH and any lipid levels. Prior statin use was not associated with outcomes. ***Conclusions:*** The admission HDL-C level was associated with favorable outcome 3 months after intravenous rt-PA therapy in stroke patients without cardioembolism.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1015–9770/12/0333–0240$38.00/0

Accessible online at:
www.karger.com/ced

Kazunori Toyoda, MD
Department of Cerebrovascular Medicine
National Cerebral and Cardiovascular Center, 5-7-1 Fujishiro-dai
Osaka 565-8565 (Japan)
Tel: +81 6 6833 5012, E-Mail toyoda@hsp.ncvc.go.jp

Introduction

Dyslipidemia is a known risk factor for ischemic stroke. High total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels and a low high-density lipoprotein cholesterol (HDL-C) level increase the risk of ischemic stroke [1–4], though low TC and LDL-C levels may increase the risk of intracerebral hemorrhage (ICH) [2, 5–7]. Lipid levels may affect stroke outcome in an opposite manner. High TC and LDL-C levels have been reported to be associated with better functional and vital outcomes after stroke [8–12]. Also, some studies showed a positive relationship between a high HDL-C level and good outcome after stroke [8, 13]. In contrast, a low LDL-C level increased the risk of early symptomatic ICH [14], and TC levels were associated with worse functional outcome in ischemic stroke patients after receiving thrombolysis or endovascular embolectomy [15]. Thus, the real contribution of lipid levels to stroke outcome, particularly after thrombolysis, is still controversial. In addition, prior use of a hydroxymethylglutaryl-CoA reductase inhibitor (statin) modifies lipid levels and makes interpretation of the contributions of lipid levels unclear.

We attempted to identify underlying risk factors that predict stroke outcomes after intravenous (i.v.) recombinant tissue plasminogen activator (rt-PA) from a multicenter observational study [Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) rt-PA Registry] [16–19]. We hypothesized that lipid levels on emergency admission were useful prognostic predictors after rt-PA. In this study, whether admission lipid levels, as well as prior statin use, were associated with early ICH and functional outcomes 3 months after rt-PA therapy in acute ischemic stroke patients was investigated.

Methods

A total of 600 consecutive patients with acute ischemic stroke who received i.v. rt-PA therapy from October 2005 to July 2008 at 10 Japanese stroke centers were enrolled in the SAMURAI rt-PA Registry. The methods and overall general results of this multicenter study have been reported previously [16]. Patients' eligibility for alteplase therapy was determined based on the Japanese guideline for i.v. rt-PA therapy [20]. 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 (not exceeding 60 mg) i.v., with 10% given as a bolus within 3 h of stroke onset followed by a continuous i.v. infusion of the remainder over 1 h. The endovascular thrombectomy devices had not been approved in Japan during this observation period, and they were not used.

Demographic factors, risk factors, cardiovascular comorbidities, medications prior to stroke onset including statins, vital signs and blood tests on emergency admission (including TC, HDL-C, LDL-C, and triglyceride levels), onset-to-treatment time, baseline National Institutes of Health Stroke Scale (NIHSS) score, and i.v. antihypertensives just before rt-PA infusion as listed in table 1 were assessed. Japanese physicians determined statin use principally based on Japan Atherosclerosis Society Guidelines [21]. Blood samples were principally taken at first assessment in the emergency room. No information about fasting or nonfasting status at the time of emergency admission was obtained. Lipid profiles were analyzed at the laboratory of each institution that was mostly checked by the Lipid Standardization Program administered by one specific laboratory (Osaka Medical Center for Health Science and Promotion). The laboratory is a member of the Cholesterol Reference Method Laboratory Network. Prior to i.v. rt-PA, all patients underwent brain computed tomography (CT) or magnetic resonance (MR) imaging. For MR examinees, early ischemic change was quantified using the Alberta Stroke Program Early CT Score (ASPECTS) on diffusion-weighted imaging (DWI), and the arterial occlusion site was identified on MR angiography as previously described [17, 22, 23]. Stroke subtype was defined according to the criteria of the Trial of Org 10172 in Acute Stroke Therapy [24], and the patients were divided into two groups: those with cardioembolism and those without.

The primary outcome was a favorable functional outcome at 3 months, corresponding to a modified Rankin Scale (mRS) score of 0 or 1. The secondary outcome was any or symptomatic ICH within the initial 36 h. Any ICH was defined as CT evidence of new ICH. Symptomatic ICH was defined according to the NINDS/Cochrane protocol as any ICH associated with neurological deterioration corresponding to an increase of ≥ 1 point from the baseline NIHSS score [14, 16], and according to the SITS-MOST [25] protocol as parenchymal hemorrhage type II combined with an increase of ≥ 4 points from the baseline NIHSS score. The examiners at the 3-month clinics were familiar with patients' stroke features in some hospitals and not in others.

Statistics

All calculations were performed using SPSS Statistics 17.0 Statistics software (IBM SPSS Inc.). A p value <0.05 was considered significant. Baseline lipid profiles and other characteristics were compared using the χ^2 test, Fisher's exact test, the unpaired t test, and the Mann-Whitney U test, as appropriate. Multivariate analysis was performed with a logistic regression model to determine whether each lipid profile was predictive of the outcomes. Since it was likely that lipid levels were highly correlated with each other, each lipid profile was separately entered into the regression model with adjustment for sex, age by forced entry, and the other nonlipid characteristics listed in table 1 by a backward selection procedure using $p > 0.10$ on the likelihood ratio test for exclusion (model 1). The analysis was also done by further adjustment with ASPECTS on DWI and occlusion of the internal carotid artery for MR examinees with supratentorial stroke (model 2). The multivariate analyses were repeated separately for patients with cardioembolism and for those without cardioembolism.

Table 1. Patients' clinical characteristics

Characteristics	Total	Prior statin		p value
		users (n = 60)	nonusers (n = 429)	
Women	171 (35.0)	19 (31.7)	152 (35.4)	0.567
Age, years	70.8 ± 11.6	72.0 ± 9.5	70.7 ± 11.9	0.420
Hypertension	300 (61.3)	47 (78.3)	253 (59.0)	0.004
Diabetes mellitus	92 (18.8)	19 (31.7)	73 (17.0)	0.007
Dyslipidemia	105 (21.5)	41 (68.3)	64 (14.9)	<0.001
Atrial fibrillation	198 (40.5)	27 (45.0)	171 (39.9)	0.447
Coronary heart disease	62 (12.7)	21 (35.0)	41 (9.6)	<0.001
Previous ischemic stroke	73 (14.9)	14 (23.3)	59 (13.8)	0.051
Prior medications				
Antithrombotics	170 (34.8)	38 (63.3)	132 (30.8)	<0.001
Antihypertensives	215 (44.0)	44 (73.3)	171 (39.9)	<0.001
Physiological data on admission				
Systolic blood pressure, mm Hg	150.9 ± 20.0	149.4 ± 21.8	151.2 ± 19.7	0.514
Diastolic blood pressure, mm Hg	81.6 ± 15.3	79.9 ± 15.6	81.8 ± 15.3	0.351
Pulse rate, bpm	79.6 ± 19.7	76.0 ± 20.2	80.2 ± 19.6	0.124
Body temperature, °C	36.3 ± 0.6	36.2 ± 0.5	36.4 ± 0.6	0.110
Laboratory data on admission				
Total cholesterol, mmol/l	4.89 ± 1.04	4.71 ± 0.84	4.92 ± 1.07	0.156
HDL-C, mmol/l	1.35 ± 0.37	1.26 ± 0.28	1.36 ± 0.38	0.022
LDL-C, mmol/l	2.95 ± 0.87	2.80 ± 0.77	2.97 ± 0.89	0.166
Triglycerides, mmol/l	1.33 ± 0.89	1.51 ± 1.14	1.30 ± 0.85	0.089
Blood glucose, mmol/l	7.65 ± 2.64	7.43 ± 2.26	7.68 ± 2.69	0.492
Creatinine, μmol/l	79.0 ± 59.8	84.5 ± 47.7	78.2 ± 61.4	0.448
Onset-to-treatment time, min	145 (122–165)	135 (120–164)	146 (125–166)	0.240
Baseline NIH Stroke Scale Score	12 (7–18)	12 (7–18)	12 (7–19)	0.687
i.v. antihypertensives just before rt-PA	139 (28.4)	18 (30.0)	121 (28.2)	0.773
Radiological findings for 402 MR examinees with supratentorial stroke				
ASPECTS on DWI ≥7	309 (76.9)	37 (74.0)	272 (77.3)	0.608
Arterial occlusion site				0.449
Internal carotid artery	68 (16.9)	11 (22.0)	57 (16.2)	
Middle cerebral artery	204 (50.7)	26 (52.0)	178 (50.6)	
Other	130 (32.3)	13 (26.0)	117 (33.2)	

Data are number of patients (%), median (interquartile range) for discontinuous variables, and mean ± SD for continuous variables.

Results

Of the 600 patients in the SAMURAI rt-PA Registry, 65 patients with a premorbid mRS score ≥2, 5 who were lost to follow-up at 3 months, and 41 who lacked information for one or more lipid levels on admission were excluded. Thus, 489 patients (171 women, 70.8 ± 11.6 years old) were included in this study. As compared with the excluded patients, the included patients more commonly took antihypertensives prior to stroke (p = 0.004) and more commonly had ASPECTS on DWI ≥7 (p = 0.020). Table 1 summarizes the patients' characteristics. Sixty patients (12.3%) used statins prior to their stroke. In these statin users, HDL-C levels were lower (1.26 ± 0.28 vs. 1.36 ± 0.38 mmol/l, p = 0.022), triglyceride levels tended to be higher (1.51 ± 1.14 vs. 1.30 ± 0.85 mmol/l, p = 0.089), and TC and LDL-C levels did not differ as compared with the remaining 429 non-statin users. Fifty-seven patients did not undergo MR imaging prior to rt-PA mainly due to contraindications, clinical instability, or time limitation. Of the remaining 432 MR examinees, 30 were diagnosed as having infratentorial strokes based on DWI and MR angiography findings.

Table 2. Lipid profiles and outcomes at 3 months

	Favorable (n = 188)	Unfavorable (n = 301)	p value	Model 1			Model 2		
				OR	95% CI	p value	OR	95% CI	p value
Dyslipidemia	43 (22.9%)	62 (20.6%)	0.551	1.03	0.63–1.67	0.917	1.18	0.68–2.07	0.557
Prior statin use	23 (12.2%)	37 (12.3%)	0.985	0.95	0.52–1.74	0.863	1.27	0.61–2.64	0.528
TC, mmol/l	4.90 ± 0.97	4.89 ± 1.09	0.937	0.98[a]	0.79–1.21[a]	0.828	0.95[a]	0.74–1.22[a]	0.687
HDL-C, mmol/l	1.39 ± 0.39	1.32 ± 0.36	0.030	1.95[a]	1.10–3.47[a]	0.023	2.03[a]	1.07–3.84[a]	0.029
LDL-C, mmol/l	2.89 ± 0.86	2.98 ± 0.88	0.305	0.84[a]	0.66–1.07[a]	0.154	0.84[a]	0.64–1.10[a]	0.195
Triglycerides, mmol/l	1.39 ± 0.98	1.29 ± 0.83	0.249	1.03[a]	0.82–1.29[a]	0.827	1.03[a]	0.77–1.36[a]	0.858

TC = Total cholesterol. Model 1, adjusted for sex, age by forced entry, diabetes mellitus, onset-to-treatment time, baseline NIHSS score, and i.v. antihypertensives chosen by a backward selection procedure in nonlipid factors listed in table 1 (except for MR findings). Model 2, adjusted for sex, age by forced entry, blood glucose, baseline NIHSS score, i.v. antihypertensives, occlusion of the internal carotid artery chosen by a backward selection procedure in nonlipid factors listed in table 1, and MR findings (ASPECTS on DWI ≥7, occlusion of the internal carotid artery).

[a] Per 1-mmol/l increase.

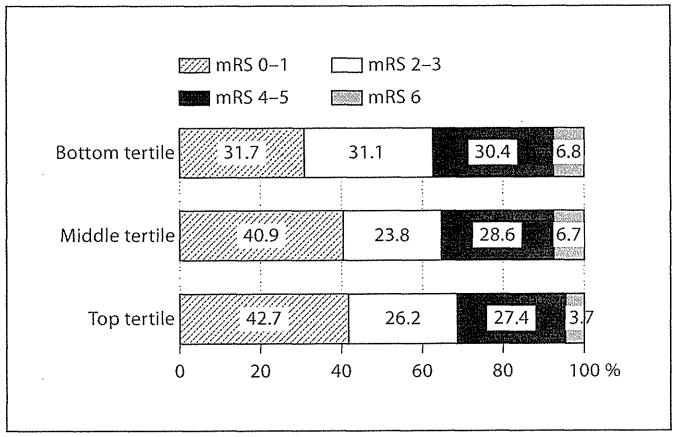

Fig. 1. mRS score at 3 months by each tertile of HDL-C level. Bottom tertile (<1.15 mmol/l): n = 161; middle tertile (1.15–1.46 mmol/l): n = 164; top tertile (≥1.46 mmol/l): n = 164.

Analyses of Overall Patients

Overall, 188 patients (38.4%) had a favorable outcome (mRS score ≤1) at 3 months. The HDL-C level was higher in patients with a favorable outcome than in those with an unfavorable outcome (1.39 ± 0.39 vs. 1.32 ± 0.36 mmol/l, p = 0.030), whereas other lipid profiles were not different between the two groups (table 2). In figure 1, the distribution of mRS scores in patients by each HDL-C level tertile is shown. The number of patients with a favorable outcome gradually increased as HDL-C levels increased. After multivariate analysis adjustment, the HDL-C level was the only lipid level that was independently related to favorable outcome (OR 1.95, 95% CI 1.10–3.47 per 1 mmol/l; p = 0.023). This relationship remained positive after further adjustment for MR findings using 402 patients who had a supratentorial stroke undergoing pretreatment MR examination (OR 2.03, 95% CI 1.07–3.84; p = 0.029).

ICH occurred in 93 patients (19.0%); 21 of these were symptomatic according to the NINDS/Cochrane definition and 4 were symptomatic according to the SITS-MOST definition. There were no significant associations between ICH and any lipid profiles on either univariate or multivariate analyses (table 3). Similarly, no lipid profiles were associated with symptomatic ICH per either definition.

Analyses of Patients with/without Cardioembolism

Stroke subtypes were cardioembolism in 302 patients (61.8%), large-artery atherosclerosis in 75 (15.3%), small-vessel occlusion in 26 (5.3%), and other types in 86 (17.6%). Of the 302 cardioembolic stroke patients, 110 (36.4%) had a favorable outcome at 3 months. On multivariate analysis, no lipid profiles were associated with a favorable outcome (e.g. OR 0.82, 95% CI 0.35–1.89 per 1 mmol/l of HDL-C).

Of the 187 stroke patients without cardioembolism, 78 (41.7%) had a favorable outcome at 3 months. On multivariate analysis, the HDL-C level (OR 4.94, 95% CI 1.91–12.76 per 1 mmol/l; p = 0.001) was independently associated with a favorable outcome.

Table 3. Lipid profiles and ICH within the initial 36 h

	Present (n = 93)	Absent (n = 396)	p value	Model 1			Model 2		
				OR	95% CI	p value	OR	95% CI	p value
Dyslipidemia	20 (21.5%)	85 (21.5%)	0.993	0.99	0.54–1.82	0.983	1.01	0.52–1.96	0.968
Prior statin use	14 (15.1%)	46 (11.6%)	0.363	1.20	0.58–2.45	0.625	1.58	0.76–3.29	0.224
TC, mmol/l	4.89 ± 1.00	4.89 ± 1.06	0.988	1.07[a]	0.85–1.36[a]	0.568	0.97[a]	0.74–1.26[a]	0.791
HDL-C, mmol/l	1.34 ± 0.34	1.35 ± 0.38	0.824	0.87[a]	0.45–1.69[a]	0.675	0.75[a]	0.35–1.58[a]	0.449
LDL-C, mmol/l	2.87 ± 0.78	2.96 ± 0.89	0.380	0.95[a]	0.72–1.25[a]	0.708	0.87[a]	0.64–1.18[a]	0.371
Triglyceride, mmol/l	1.34 ± 1.18	1.32 ± 0.81	0.891	1.12[a]	0.85–1.47[a]	0.419	1.16[a]	0.87–1.53[a]	0.307

TC = Total cholesterol. Model 1, adjusted for sex, age by forced entry, diabetes mellitus, atrial fibrillation, prior antithrombotics, blood glucose, and i.v. antihypertensives chosen by a backward selection procedure in nonlipid factors listed in table 1 (except for MR findings). Model 2, adjusted for sex, age by forced entry, diabetes mellitus, atrial fibrillation, prior antithrombotics, blood glucose, onset-to-treatment time, i.v. antihypertensives, occlusion of the internal carotid artery chosen by a backward selection procedure in nonlipid factors listed in table 1, and MR findings (ASPECTS on DWI ≥7, occlusion of the internal carotid artery).

[a] Per 1-mmol/l increase.

Discussion

In this study, the effects of admission lipid levels and prior statin use on clinical outcomes in stroke patients receiving i.v. rt-PA were examined. The major finding of this study was that a higher HDL-C level was associated with completely independent activities of daily living at 3 months after multivariate adjustment for clinical and radiological characteristics. The association was clear in patients without cardioembolism, but was not confirmed in cardioembolic stroke patients. In the present cohort, no relationships between functional outcome and other lipid levels or prior statin use were identified. Besides, any lipid levels or prior statin use were not related to ICH.

Although HDL-C is a potent protective factor for cardiovascular diseases and stroke, it may be understudied as compared with LDL-C. HDL-C has not only a direct role against atherosclerosis to remove free cholesterol from macrophages in the arterial wall and return it to the liver, but it also inhibits prothrombotic and proinflammatory phenomena [26, 27]. In addition, HDL-C protects LDL from oxidation, promotes endothelial nitric oxide synthesis, and increases vasodilatation [26, 28]. These manifold effects, including antiatherosclerotic, vasoprotective, and neuroprotective effects, have been assumed to improve stroke outcome. Interestingly, the statistical significance of the contribution of HDL-C to favorable outcome was much higher in stroke patients without cardioembolism than overall patients, although the number of patients was much smaller. This result suggests that HDL-C has a larger protective effect for patients with atherothrombotic conditions. In contrast, LDL-C was not a predictor of a favorable outcome. Prior statin use in some patients might modify admission LDL-C levels and affect the results. Since the purpose of the present study was to assess the significance of lipid levels on emergency admission as a prognostic predictor, the fasting status of patients on admission was not considered relevant. Although the HDL-C level is little influenced by fasting or nonfasting, the LDL-C level appears to be influenced to some extent [29].

Statin use prior to stroke onset was reported to improve functional outcomes of general ischemic stroke patients [30–33]. For stroke patients treated with i.v. rt-PA, one study reported a positive association between statin use and favorable 3-month outcome [34], though another study found no such association [35]. The studies on thrombolysis including intra-arterial thrombolysis or endovascular intervention introduced a warning message that prior statin use and a low LDL-C level increased symptomatic ICH after treatment [14, 36]. In the present cohort, neither statin use nor any lipid levels were associated with ICH, which was also observed in previous studies only for patients treated with i.v. rt-PA [34, 35]. The discrepancies of results between the former studies and ours may be caused by the difference of not only treatment but baseline features. In our study, statin users had uncommonly hypertension compared with those in Meier et al. [36] (78.3 vs. 92.6%), and patients with LDL-C levels <85 mg/dl (2.20 mmol/l) were fewer than those in Bang et al. [14] (19.0 vs. 33%). Also, a lower dose of alteplase (0.6 mg/kg) than the standard Western dose may

result in relatively few ICH events and affect the statistical analysis, but prior statin use seems to be safe for Japanese patients receiving i.v. rt-PA.

A unique point was that statin use seems to be less prevalent in Japan than in Western countries. Statin users prior to ischemic stroke onset accounted for 13.6–16.5% in Japanese multicenter prospective observational studies [37, 38], as compared to 18–23% in Western studies [15, 30–34]. The major reason for this less prevalence is that Japanese relatively uncommonly have dyslipidemia (21.5% in our study, 21% in the SUMO study [39] from Japan vs. 29–36% in Western studies [15, 30–34]) and coronary artery diseases (12.7% in ours, 12% in the SUMO study [39] vs. 18–32% in Western studies [15, 30–34]) possibly due to the difference in ethnic and dietary habit.

Previous studies showed the lower HDL-C levels and higher triglyceride levels in statin users than non-users [32, 36], and our results were similar. Statin increased HDL-C levels in some reports [40, 41], and did not in another [42]. Thus, the therapeutic effect of statin on HDL-C does not seem to be as clear as that on LDL-C. Another possible reason for lower HDL-C levels in our statin users was that their HDL-C levels prior to statin medication might be too low. Anyway, premorbid statin use could make the association of HDL-C levels to stroke outcomes complicated.

The strengths of this study included that it was a multicenter study with frequent use of MR techniques. On the other hand, it had several limitations. First, this study only included patients treated with rt-PA. Thus, the present results could not be compared with those in patients not receiving rt-PA. Second, this study was a retrospective observational study, and 46 patients were excluded from the analysis because of lack of data on admission lipid levels or 3-month mRS scores. The excluded patients had different baseline features from included ones to some extent, and this may have caused selection bias. Third, we did not have complete information on doses and duration of prior statin use. Also, the information on initiation and continuation of statin use after stroke onset was incomplete, and we could not assess the effects of them on clinical outcome.

Although HDL-C seems to be a promising outcome predictor after i.v. rt-PA, it is not clear if HDL-C level raising therapy prior to stroke or during the acute stroke improves stroke outcomes. Recently, pharmacotherapy other than statins to increase directly HDL-C levels is developing [43, 44]. The future studies to examine whether increasing HDL-C levels prevent and improve stroke are desired.

Acknowledgment

This study was supported by a grant-in-aid (H20-Junkanki-Ippan-019 and H23-Junkanki-Ippan-010) from the Ministry of Health, Labour and Welfare, Japan, and received research funding from the National Cerebral and Cardiovascular Center (22-4-1).

Disclosure Statement

Dr. Nakagawara receives honoraria from Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin, and Lundbeck. Dr. Okada receives an honorarium from Mitsubishi Tanabe Pharma and a consulting fee from Lundbeck. Dr. Toyoda receives research support from Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan.

References

1 Kurth T, Everett BM, Buring JE, Kase CS, Ridker PM, Gaziano JM: Lipid levels and the risk of ischemic stroke in women. Neurology 2007;68:556–562.

2 Tirschwell DL, Smith NL, Heckbert SR, Lemaitre RN, Longstreth WT Jr, Psaty BM: Association of cholesterol with stroke risk varies in stroke subtypes and patient subgroups. Neurology 2004;63:1868–1875.

3 Amarenco P, Labreuche J, Touboul PJ: High-density lipoprotein-cholesterol and risk of stroke and carotid atherosclerosis: a systematic review. Atherosclerosis 2008;196:489–496.

4 Amarenco P, Goldstein LB, Callahan A 3rd, Sillesen H, Hennerici MG, O'Neill BJ, Rudolph AE, Simunovic L, Zivin JA, Welch KMA; on behalf of the SPARCL Investigators: Baseline blood pressure, low- and high-density lipoproteins, and triglycerides and the risk of vascular events in the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Atherosclerosis 2009;204:515–520.

5 The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators: High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549–559.

6 Leppälä JM, Virtamo J, Fogelholm R, Albanes D, Heinonen OP: Different risk factors for different stroke subtypes: association of blood pressure, cholesterol, and antioxidants. Stroke 1999;30:2535–2540.

7 Sturgeon JD, Folsom AR, Longstreth WT Jr, Shahar E, Rosamond WD, Cushman M: Risk factors for intracerebral hemorrhage in a pooled prospective study. Stroke 2007;38:2718–2725.

8 Li W, Liu M, Wu B, Liu H, Wang LC, Tan S: Serum lipid levels and 3-month prognosis in Chinese patients with acute stroke. Adv Ther 2008;25:329–341.

9 Cuadrado-Godia E, Jiménez-Conde J, Ois A, Rodríguez-Campello A, García-Ramallo E, Roquer J: Sex differences in the prognostic value of the lipid profile after the first ischemic stroke. J Neurol 2009;256:989–995.
10 Vauthey C, de Freitas GR, van Melle G, Devuyst G, Bogousslavsky J: Better outcome after stroke with higher serum cholesterol levels. Neurology 2000;54:1944–1949.
11 Dyker AG, Weir CJ, Lees KR: Influence of cholesterol on survival after stroke: retrospective study. BMJ 1997;314:1584–1588.
12 Olsen TS, Christensen RHB, Kammersgaard LP, Andersen KK: Higher total serum cholesterol levels are associated with less severe strokes and lower all-cause mortality: ten-year follow-up of ischemic strokes in the Copenhagen Stroke Study. Stroke 2007;38: 2646–2651.
13 Newman GC, Bang H, Hussain SI, Toole JF: Association of diabetes, homocysteine, and HDL with cognition and disability after stroke. Neurology 2007;69:2054–2062.
14 Bang OY, Saver JL, Liebeskind DS, Starkman S, Villablanca P, Salamon N, Buck B, Ali L, Restrepo L, Vinuela F, Duckwiler G, Jahan R, Razinia T, Ovbiagele B: Cholesterol level and symptomatic hemorrhagic transformation after ischemic stroke thrombolysis. Neurology 2007;68:737–742.
15 Restrepo L, Bang OY, Ovbiagele B, Ali L, Kim D, Liebeskind DS, Starlman S, Vinuela F, Duckwiler GR, Jahan R, Saver JL: Impact of hyperlipidemia and statins on ischemic stroke outcomes after intra-arterial fibrinolysis and percutaneous mechanical embolectomy. Cerebrovasc Dis 2009;28:384–390.
16 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; for the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI) 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.
17 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.
18 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 outcome 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.
19 Koga M, Kimura K, Shibazaki K, Shiokawa Y, Nakagawara J, Furui E, Yamagami H, Okada Y, Hasegawa Y, Kario K, Okuda S, Naganuma M, Nezu T, Maeda K, Minematsu K, Toyoda K: CHADS2 score is associated with 3-month clinical outcomes after intravenous rt-PA therapy in stroke patients with atrial fibrillation: SAMURAI rt-PA Registry. J Neurol Sci 2011;306:49–53.
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 Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, Daida H, Biro S, Hirobe K, Funahashi T, Yokote K, Yokode M: Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. J Atheroscler Thromb 2007;14:45–50.
22 Barber PA, Hill MD, Eliasziw M, Demchuk AM, Pexman JHW, Hudon ME, Tomanek A, Frayne R, Buchan AM; for the ASPECTS Study Group: 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.
23 Nakashima T, Toyoda K, Koga M, Matsuoka H, Nagatsuka K, Naritomi H, Minematsu K: 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.
24 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.
25 Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G; for the SITS-MOST investigators: Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet 2007;369:275–282.
26 Sanossian N, Saver JL, Navab M, Ovbiagele B: High-density lipoprotein cholesterol: an emerging target for stroke treatment. Stroke 2007;38:1104–1109.
27 Lapergue B, Moreno JA, Dang BQ, Coutard M, Delbosc S, Raphaeli G, Auge N, Klein I, Mazighi M, Michel JB, Amarenco P, Meilhac O: Protective effect of high-density lipoprotein-based therapy in a model of embolic stroke. Stroke 2010;41:1536–1542.
28 Paternò R, Ruocco A, Postiglione A, Hubsch A, Andresen I, Lang MG: Reconstituted high-density lipoprotein exhibits neuroprotection in two rat models of stroke. Cerebrovasc Dis 2004;17:204–211.
29 Wilder LB, Bachorik PS, Finney CA, Moy TF, Becker DM: The effect of fasting status on the determination of low-density and high-density lipoprotein cholesterol. Am J Med 1995;99:374–377.
30 Martí-Fàbregas J, Gomis M, Arboix A, Aleu A, Pagonabarraga J, Belvís R, Cocho D, Roquer J, Rodríguez A, García MD, Molina-Porcel L, Díaz-Manera J, Martí-Vilalta JL: Favorable outcome of ischemic stroke in patients pretreated with statins. Stroke 2004; 35:1117–1123.
31 Reeves MJ, Gargano JW, Luo Z, Mullard AJ, Jacobs BS, Majid A; for the Paul Coverdell National Acute Stroke Registry Michigan Prototype Investigators: Effect of pretreatment with statins on ischemic stroke outcomes. Stroke 2008;39:1779–1785.
32 Yoon SS, Dambrosia J, Chalela J, Ezzeddine M, Warach S, Haymore J, Davis L, Baird AE: Rising statin use and effect on ischemic stroke outcome. BMC Med 2004;2:4.
33 Arboix A, García-Eroles L, Oliveres M, Targa C, Balcells M, Massons J: Pretreatment with statins improves early outcome in patients with first-ever ischaemic stroke: a pleiotropic effect of statins or a beneficial effect of hypercholesterolemia? BMC Neurol 2010;10: 47.
34 Álvarez-Sabín J, Huertas R, Quintana M, Rubiera M, Delgado P, Ribó M, Molina CA, Montaner J: Prior statin use may be associated with improved stroke outcome after tissue plasminogen activator. Stroke 2007;38: 1076–1078.
35 Miedema I, Uyttenboogaart M, Koopman K, De Keyser J, Luijckx GJ: Statin use and functional outcome after tissue plasminogen activator treatment in acute ischaemic stroke. Cerebrovasc Dis 2010;29:263–267.
36 Meier N, Nedeltchev K, Brekenfeld C, Galimanis A, Fischer U, Findling O, Remonda L, Schroth G, Mattle HP, Arnold M: Prior statin use, intracranial hemorrhage, and outcome after intra-arterial thrombolysis for acute ischemic stroke. Stroke 2009;40:1729–1737.
37 Kuwashiro T, Sugimori H, Kamouchi M, Ago T, Kitazono T, Iida M: Lower levels of high-density lipoprotein cholesterol on admission and a recurrence of ischemic stroke: a 12-month follow-up of the Fukuoka Stroke Registry. J Stroke Cerebrovasc Dis 2011, E-pub ahead of print.
38 Matsumoto S, Nomura E, Ohtsuki T, Kohriyama T, and J-STARS Investigators: Statin trial for secondary prevention of ischemic stroke: J-STARS. Jpn J Stroke 2005;27:474–479.

39 Sato S, Uehara T, Toyoda K, Yasui N, Hata T, Ueda T, Okada Y, Toyota A, Hasegawa Y, Naritomi H, Minematsu K, and the Stroke Unit Multicenter Observational (SUMO) Study Group: Impact of the approval of intravenous recombinant tissue plasminogen activator therapy on the processes of acute stroke management in Japan: the SUMO study. Stroke 2009;40:30–34.
40 Chapman MJ: Are the effects of statins on HDL-cholesterol clinically relevant? Eur Heart J 2004;6(suppl C):C58.
41 Chyu KY, Peter A, Shah PK: Progress in HDL-based therapies for atherosclerosis. Curr Atheroscler Rep 2011;13:405–412.
42 LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJP, Shepherd J, Wenger NK, for the Treating to New Targets (TNT) Investigators: Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005;352:1425–1435.
43 Stein EA, Stroes ESG, Steiner G, Buckley BM, Capponi AM, Burgess T, Niesor EJ, Kallend D, Kastelein JJP: Safety and tolerability of dalcetrapib. Am J Cardiol 2009;104:82–91.
44 Cannon CP, Shah S, Dansky HM, Davidson MD, Brinton EA, Gotto AM Jr, Stepanavage M, Liu SX, Gibbons P, Ashraf TB, Zafarino J, Mitchel Y, Barter P; for the DEFINE Investigators: Safety of anacetrapib in patients with or at high risk for coronary heart disease. N Engl J Med 2010;363:2406–2415.

Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2011;31:123–129
DOI: 10.1159/000321516

Received: March 2, 2010
Accepted: September 15, 2010
Published online: November 17, 2010

Reduced Estimated Glomerular Filtration Rate Is Associated with Stroke Outcome after Intravenous rt-PA: The Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA Registry

Masaki Naganuma[a] Masatoshi Koga[a] Yoshiaki Shiokawa[b] Jyoji Nakagawara[d] Eisuke Furui[e] Kazumi Kimura[f] Hiroshi Yamagami[g] Yasushi Okada[h] Yasuhiro Hasegawa[i] Kazuomi Kario[j] Satoshi Okuda[k] Kazutoshi Nishiyama[c] Kazuo Minematsu[a] Kazunori Toyoda[a]

[a]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Departments of [b]Neurosurgery and [c]Neurology, Stroke Center, Kyorin University School of Medicine, Mitaka, [d]Department of Neurosurgery and Stroke Center, Nakamura Memorial Hospital, Sapporo, [e]Department of Stroke Neurology, Kohnan Hospital, Sendai, [f]Department of Stroke Medicine, Kawasaki Medical School, Kurashiki, [g]Stroke Center, Kobe City Medical Center General Hospital, Kobe, [h]Department of Cerebrovascular Diseases, National Hospital Organization, Kyushu Medical Center, Fukuoka, [i]Department of Neurology, St. Marianna University School of Medicine, Kawasaki, [j]Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Shimotsuke, and [k]Department of Neurology, National Hospital Organization, Nagoya Medical Center, Nagoya, Japan

Key Words
Infarction · Intracerebral hemorrhage · Renal dysfunction · rt-PA · SAMURAI

Abstract
Background: The aim of this study was to determine whether renal dysfunction affects the outcome of stroke patients treated with recombinant tissue plasminogen activator (rt-PA). ***Methods:*** A retrospective, multicenter, observational study was conducted to identify the effects of underlying risk factors on intravenous rt-PA therapy using 0.6 mg/kg alteplase in 10 stroke centers in Japan. Consecutive stroke patients with a premorbid modified Rankin Scale (mRS) score ≤3 who received rt-PA were studied. Renal dysfunction was defined as estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 on admission. The outcome measures were any intracerebral hemorrhage (ICH) and symptomatic ICH within the initial 36 h; favorable (mRS 0–1) outcome, poor outcome (mRS 4–6) and mortality at 3 months. ***Results:*** Of a total of 578 patients (372 men; 64.4%, 71.4 ± 11.7 years old), renal dysfunction was present in 186 patients (32.2%). These patients were older and more commonly had hypertension, atrial fibrillation, prior ischemic heart disease and prior use of antithrombotic agents than patients without renal dysfunction. ICH (27.4 vs. 16.6%) and symptomatic ICH (8.1 vs. 2.6%) was more common in patients with renal dysfunction than in those without. At 3 months, patients with renal dysfunction had higher median mRS scores than those without (3 vs. 2). After multivariate adjustment for established outcome predictors, renal dysfunction was related to any ICH (odds ratio 1.81, 95% confidence interval 1.16–2.84), symp-

KARGER
Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1015–9770/11/0312–0123$38.00/0

Accessible online at:
www.karger.com/ced

Kazunori Toyoda, MD
Department of Cerebrovascular Medicine
National Cerebral and Cardiovascular Center
Fujishirodai 5-7-1, Suita, Osaka 565-8565 (Japan)
Tel. +81 6 6833 5012, Fax +81 6 6872 7486, E-Mail toyoda@hsp.ncvc.go.jp

tomatic ICH (2.64, 1.10–6.56), poor outcome (1.55, 1.01–2.38), and mortality (2.94, 1.38–6.42). ***Conclusions:*** Reduced eGFR was associated with early ICH and 3-month unfavorable outcome in stroke patients receiving intravenous rt-PA.

Introduction

Renal dysfunction is increasingly noted as a risk factor for stroke in the general population [1, 2], as well as in high-risk patients having diabetes mellitus [3], essential hypertension [4], and preexisting atherothrombotic disease [5, 6]. In a large cohort of patients with acute stroke, renal dysfunction was an independent predictor for long-term mortality and poor outcome [7–9].

Though intravenous (IV) thrombolysis is a standard therapy for acute stroke patients, the effect of renal dysfunction on vital and functional outcome measures following therapy is inconclusive. As far as we know, only one study (involving 196 stroke patients) reported that a high admission serum creatinine level was independently predictive of a modified Rankin scale (mRS) score ≥3 at 3 months after IV recombinant tissue plasminogen activator (rt-PA) [10]. This study also reported that an impaired estimated glomerular filtration rate (eGFR), defined as <90 ml/min/1.73 m^2, tended to be associated with symptomatic intracerebral hemorrhage (ICH). Since renal dysfunction appears to be an important predictor for stroke outcome, its significance for rt-PA-treated patients should be ascertained in a larger cohort using a multicenter design.

To identify adequate risk factor control in acute stroke patients treated with thrombolysis, a multicenter study group [Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) Study Group] was formed. Here, we determined the association of renal dysfunction based on admission eGFR with stroke outcome after IV rt-PA using the database of this study group.

Patients and Methods

The SAMURAI rt-PA Registry Trial had a multicenter, hospital-based, retrospective, observational, cohort design [11]. Details of this study have been described previously [11, 12]. In brief, this study involved 600 consecutive patients with acute ischemic stroke receiving IV rt-PA from October 2005 to July 2008. Of these, 22 patients were ineligible for analysis; 17 patients had dependent activity of daily living before onset, corresponding to an mRS score ≥4, and 5 patients had incomplete 3-month mRS score data. Thus, the remaining 578 patients were included in the present study. Each local ethics committee approved the research protocol. Each patient received a single IV alteplase dose of 0.6 mg/kg, with 10% given as a bolus within 3 h of stroke onset, followed by a continuous IV infusion of the remainder over 1 h [13].

From the database of the SAMURAI rt-PA registers, the data listed in table 1 were extracted for this study. Neurological deficits were assessed using the National Institutes of Health Stroke Scale (NIHSS) score just before and 24 h after rt-PA. Ischemic stroke subtype according to the TOAST categories was elucidated based on information of non-contrast computed tomography (CT), diffusion-weighted magnetic resonance imaging (MRI), magnetic resonance angiography, CT angiography, cervical/transcranial ultrasound, transthoracic or transesophageal echocardiography, and 24-hour Holter monitoring in addition to neurological findings [14].

Kidney function was evaluated based on the eGFR using a revised equation for the Japanese population [15]; eGFR (ml/min/1.73 m^2) = 194 × (serum creatinine)$^{-1.094}$ × (age)$^{-0.287}$ × 0.739 (for women). To calculate eGFR, admission serum creatinine was used. According to the Kidney Disease Outcomes Quality Initiative guidelines of the National Kidney Foundation [16], renal dysfunction was defined as a reduced eGFR (<60 ml/min/1.73 m^2). The stage of renal dysfunction was classified as follows: stage 3 (eGFR 30–59 ml/min/1.73 m^2), stage 4 (15–29 ml/min/1.73 m^2), and stage 5 (<15 ml/min/1.73 m^2 or dialysis).

The major outcome measures were: any ICH defined as CT or MRI evidence of new ICH within the initial 36 h; symptomatic ICH with neurological deterioration corresponding to an increase of ≥1 point from the baseline NIHSS score (Cochrane/National Institute of Neurological Disorders and Stroke definition); favorable and poor outcome at 3 months, and mortality at 3 months. To assess favorable and poor outcome, definitions in the subanalyses of the National Institute of Neurological Disorders and Stroke rt-PA Trial (an mRS of 0–1 and 4–6, respectively) were used [17–20].

Statistical Analysis

Statistical test results were considered significant if $p < 0.05$. All analyses were performed using JMP statistical software (version 7.0.1; SAS Institute, Cary, N.C., USA). Baseline clinical characteristics and stroke features were compared using Student's unpaired t test for parametric continuous variables, Mann-Whitney's U test for nonparametric variables, and Fisher's exact test and the χ^2 test for categorical variables. To identify independent predictors of ICH within 36 h and stroke outcome at 3 months, multivariate logistic regression analysis was performed. For each outcome, sex, age, and renal dysfunction were initially entered, and the other variables listed in table 1 were chosen by a backward selection procedure using $p > 0.10$ in the likelihood ratio test for exclusion.

Results

A total of 578 patients (372 men, 71.4 ± 11.7 years old) were studied. Of these, 186 (32.2%) patients had renal dysfunction with eGFR <60 ml/min/1.73 m^2; 163 (28.2%)

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

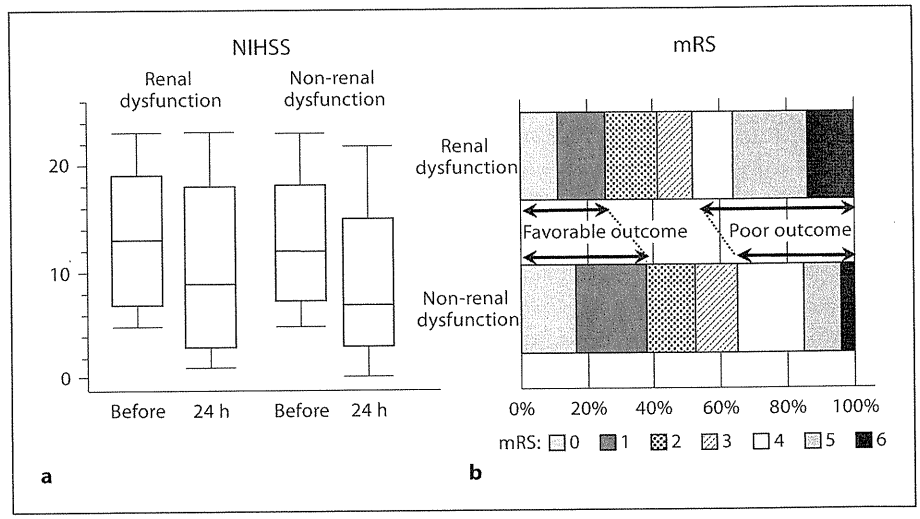

Fig. 1. Neurological deficits and outcome of patients with and without renal dysfunction. NIHSS score just before and 24 h after IV rt-PA therapy (**a**) and mRS score at 3 months (**b**) in patients with and without renal dysfunction. **a** Horizontal lines in boxes = Median NIHSS score; boxes = IQR;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

Disclosure Statement

M.K. received a grant from the Japan Cardiovascular Research Foundation (The Bayer Scholarship for Cardiovascular Research). J.N. received honoraria from Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin, and Lundbeck. Y.O. received a honorarium from Mitsubishi Tanabe Pharma and a consulting fee from Lundbeck. K.M. received research support from the Ministry of Health, Labour and Welfare, Japan, research grants for cardiovascular diseases, grant-in-aid, the Foundation for Biomedical Research and Innovation, Mitsubishi Tanabe Pharma Corporation, and Kyowa Hakko Kirin Pharma, Inc., Hitachi Medical Corporation. K.T. received research support from grants-in-aid (H20-Junknaki-Ippan-019) from the Ministry of Health, Labour and Welfare, Japan.

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.

Original Paper

European Neurology

Eur Neurol 2011;66:37–41
DOI: 10.1159/000328792

Received: December 14, 2010
Accepted: April 26, 2011
Published online: June 28, 2011

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

Masaki Naganuma[a] Mayumi Mori[a, b] Tomohisa Nezu[a] Noriko Makihara[b] Masatoshi Koga[a] Yasushi Okada[b] Kazuo Minematsu[a] Kazunori Toyoda[a] on behalf of the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) Study Investigators

[a]Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, and
[b]Department of Cerebrovascular Disease, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

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].

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0014–3022/11/0661–0037$38.00/0

Accessible online at:
www.karger.com/ene

Kazunori Toyoda, MD
Department of Cerebrovascular Medicine
National Cerebral and Cardiovascular Center
Fujishirodai 5-7-1, Suita 565-8565 (Japan)
Tel. +81 6 6833 5012, E-Mail toyoda@hsp.ncvc.go.jp

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

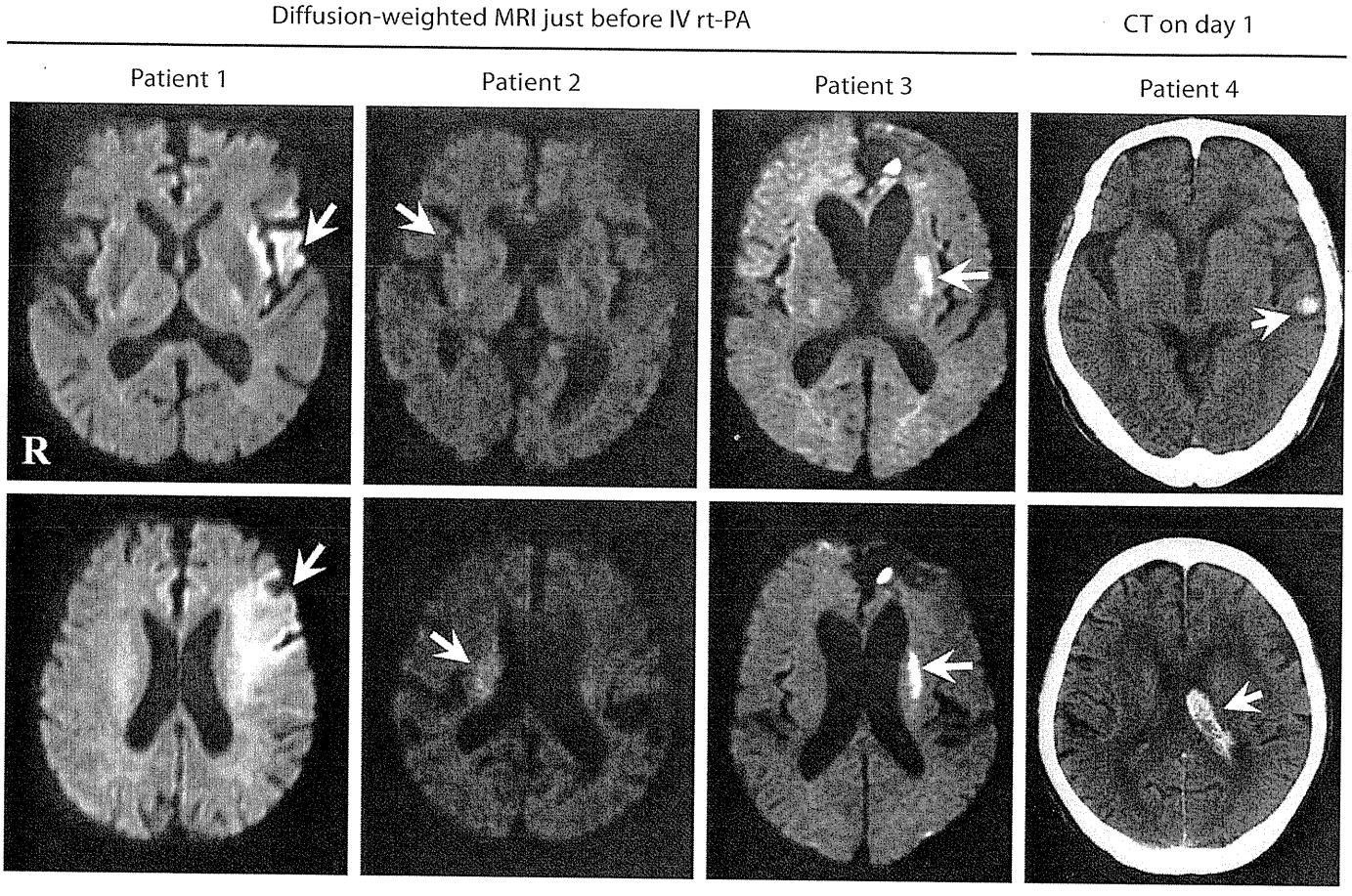

Fig. 1. DWI just before IV rt-PA therapy in patients 1–3, and CT on the day of thrombolysis in patient 4. Arrows show early ischemic changes or ectopic hemorrhage.

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-