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EDITORIAL

Is Anticoagulant Therapy Unnecessary for Lower-Risk Japanese Patients With Atrial Fibrillation?

– Lessons From the SAMURAI-NVAF and BAT Studies –

Kazunori Toyoda, MD, PhD

When considering anticoagulation for patients with nonvalvular atrial fibrillation (NVAF) who have relatively low $CHADS_2$ and CHA_2DS_2-VASc scores, cardiologists, who are mainly interested in primary prevention of major events, and neurologists, who treat cardioembolism patients, have different perspectives. For cardiologists, it is often difficult to continue anticoagulation for many target patients without the development of bleeding complications. The neurologists often complain when they see victims of underuse or underdosing of anticoagulation. **Figure 1** shows the percentages of patients with low (0), intermediate (1), and high (≥2) $CHADS_2$ scores who were registered in the prospective, multicenter, Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-NVAF Study.[1] In this study, 1,192 patients with NVAF within 7 days after onset of ischemic stroke or transient ischemic attack (TIA) were enrolled between September 2011 and March 2014. The percentage of patients who took oral anticoagulant drugs prior to the index stroke/TIA was only 36.8%, even among the high-$CHADS_2$ score patients. Although the main reason for the absence of anticoagulation therapy was lack of identification of NVAF prior to the index stroke/TIA, ≥30% of the patients in any of the low-, intermediate-, and high-risk groups were not taking anticoagulant drugs, even though NVAF had been detected.

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In this issue of the Journal, Suzuki and colleagues[2] report how they determined the stroke risk in Japanese NVAF patients not on anticoagulation, based on a pooled analysis of 3,588 patients from the Shinken Database,[3] J-RHYTHM Registry,[4,5]

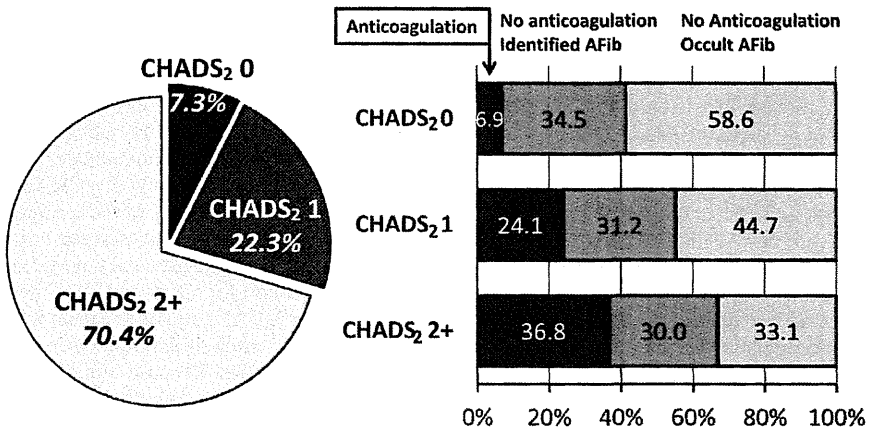

Figure 1. (**Left**) Percentages of patients with low (0), intermediate (1), and high (≥2) $CHADS_2$ scores prior to onset of index stroke or transient ischemic attack (TIA) who did or did not receive prestroke anticoagulation: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-nonvalvular atrial fibrillation (NVAF) Study. (**Right**) Percentages of patients who received anticoagulation, those without anticoagulation despite atrial fibrillation being identified, and those without anticoagulation and atrial fibrillation not identified (Occult AFib) prior to index stroke/TIA in each ischemia risk category.

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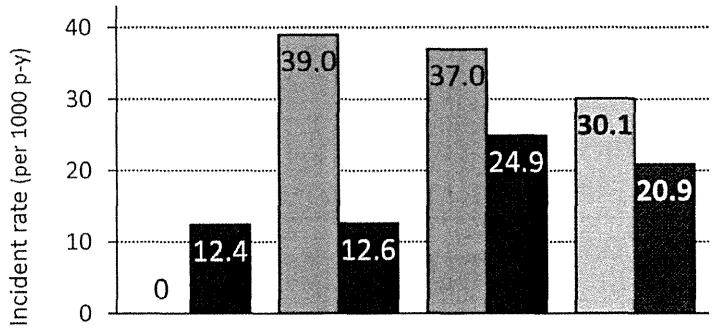

	CHADS$_2$ 0		CHADS$_2$ 1		CHADS$_2$ 2+		Overall	
	No AC	AC	No AC	AC	No AC	AC	**No AC**	**AC**
No. of events	0	2	2	4	3	25	**5**	**31**
No. of patients	24	106	34	215	55	652	**113**	**973**
Person-years	34	161	51	318	81	1005	**166**	**1484**

Figure 2. Rate of ischemic stroke in patients with and without anticoagulation (AC) according to ischemia risk by the CHADS2 score: the Bleeding with Antithrombotic Therapy (BAT) Study.

and Fushimi AF Registry.[6,7] The incidence of ischemic stroke was 13.3 per 1,000 person-years overall, and 5.4, 9.3, and 24.7 per 1,000 person-years, respectively, in the low-, intermediate-, and high-risk categories of CHADS2 scores. The rates, especially in the lower-risk categories, were unexpectedly low, for example, as compared with those from the results of the Bleeding with Antithrombotic Therapy (BAT) Study.[8,9] The BAT study included 4,009 patients from 19 hospitals in Japan who were taking oral antiplatelet agents or warfarin for cardiovascular or cerebrovascular disease between October 2003 and March 2006. Of these, 1,221 patients had AF, and their annual incidence of ischemic stroke was 0.76%, 1.46%, and 2.90% in the respective risk categories based on CHADS2 score.[10] **Figure 2** shows how the stroke risk was re-analyzed using 1,086 patients with NVAF in the BAT register. The distribution of low, intermediate, and high CHADS2 score was 12.0%, 22.9%, and 65.1%, respectively, in patients without anticoagulation. The incidence of ischemic stroke in the overall patients without anticoagulation was 30.1 per 1,000 person-years; the incidence reached 39.0 per 1,000 person-years when the patients were limited to the intermediate risk category. These rates were similar to those from the first validation cohort for the CHADS2 score,[11] the Euro Heart Survey,[12] and a Japanese study by Inoue et al.[13]

Why is the stroke risk different in the study by Suzuki et al[2] and the previous ones, including the BAT study?[11–13] A possible reason is the decade-long difference in the medical environment, including the management of coexisting diseases, as Suzuki et al discuss. Because NVAF was not the primary theme of the BAT study, there may be limitations in using the BAT cohort for analysis of stroke risk in NVAF patients. Nevertheless, the relatively low stroke risk in the lower-risk NVAF patients shown by Suzuki et al using the 3 major Japanese databases might be somewhat optimistic as compared with the real world.

It would be undesirable if NVAF patients with a CHADS2 score of 1 were not given anticoagulation based solely on the findings of this study. Suzuki et al stress that the important point of their study is the higher incidence of ischemic stroke in patients with CHADS2 score ≥2, not the low incidence in those with CHADS2 score ≤1. Among components corresponding to the CHADS2 score of 1, hypertension, diabetes, and congestive heart failure are modifiable, but aging is not. Aging was most strongly related to stroke risk among the 4 components in the study by Suzuki et al. In the Loire Valley Atrial Fibrillation Project, the incidence of stroke was 32.6 per 1,000 person-years in NVAF patients ≥75 years old without any other CHADS2 risk factors who did not receive anticoagulation.[14] Thus, anticoagulation is necessary for such patients. To put it the other way around, the recommendation for anticoagulation for NVAF patients <75 years with a CHADS2 score of 1 might be weakened in the future by further progress in therapeutic strategies against hypertension, diabetes, or heart failure.

The pooled cohort from the 3 major Japanese databases is a desirable cohort for clarifying the appropriate anticoagulation therapy for NVAF patients in Japan, where both ischemic and hemorrhagic strokes are relatively more common than in Western countries. Because 2 of these 3 studies are ongoing, we will obtain further useful findings from these databases in the future.

Disclosures

None.

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CASE REPORT

Ultra-early intravenous thrombolytic therapy for recurrent ischemic stroke after transient ischemic attack

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Key words
cerebral embolism, cerebrovascular stroke, elderly, therapeutic thrombolysis, time to treatment.

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Abstract

An 89-year-old woman was admitted to our stroke care unit because of transient ischemic attack caused by cardioembolic occlusion of the right internal carotid artery. She developed recurrent ischemic stroke shortly after hospitalization. She was very quickly treated with intravenous tissue plasminogen activator, because she had been just hospitalized, and had a favorable outcome. Earlier thrombolysis to patients with ischemic stroke is associated with better outcomes. Hospitalization in a stroke care unit is useful for close observation of patients with transient ischemic attack, and allows timely administration of tissue plasminogen activator.

Introduction

The care of patients with transient ischemic attack (TIA) can be adequately achieved in the outpatient clinic.[1] In contrast, there is an assertion that high-risk patients with TIA as a result of arterial stenosis or cardioembolic sources should be immediately admitted to the hospital irrespective of the ABCD[2] score,[2] because hospitalized patients might be more likely to receive not only the best medical treatment, but also thrombolytic therapy and carotid revascularization.[3] We report the case of a patient with TIA as a result of cardioembolic occlusion of the internal carotid artery (ICA) who developed recurrent ischemic stroke (IS) shortly after hospitalization and was very quickly treated with intravenous thrombolysis.

Case report

An 89-year-old woman presented to the Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan, complaining of a transient episode of left facial drooping and slurred speech 90 min after onset of symptoms. She had undergone pacemaker implantation because of sick sinus syndrome, and had taken warfarin for atrial fibrillation. Neurological examination showed no abnormalities on presentation. Coagulation testing showed an international normalized ratio of 1.07, within the normal range. Carotid ultrasonography showed no diastolic flow, indicating distal occlusion in the right ICA (Fig. 1a). We speculated that neurological deficits had disappeared because the right Middle Cerebral Artery (MCA) was sufficiently perfused by collateral supply through the anterior or posterior communicating arteries, although transcranial color-coded sonography could not be carried out because of a poor transtemporal acoustic window. Cardiogenic TIA was diagnosed and the patient was hospitalized 30 min after presenting to the emergency room. However, she suddenly developed disturbance of consciousness, conjugate gaze deviation to the right and left hemiparesis 3 h after admission to the stroke care unit. The National Institute of Health Stroke Scale (NIHSS) score was 24. This deterioration was attributed to recurrent IS resulting from disturbed blood flow in the right MCA after distal migration of the cardiogenic embolus. Because head computed tomography showed no extensive early ischemic changes (Fig. 1d), intravenous tissue plasminogen activator (tPA) was administered 34 min after the development of recurrent IS. Symptoms improved dramatically during thrombolysis. Carotid ultrasonography showed the appearance of diastolic flow, which indicated recanalization in the occluded ICA, 30 min after initiating thrombolysis (Fig. 1b). At 24 h after thrombolysis, the NIHSS score was 2 and blood flow of the ICA on carotid ultrasonography was normalized (Fig. 1c). Follow-up computed tomography clearly showed right putaminal infarction (Fig. 1e). The modified Rankin Scale score at the time of discharge was 1.

Discussion

The present patient was able to be treated with tPA very shortly after recurrent IS because of her hospitalization, and outcomes were favorable without hemorrhagic complications. Previous analysis has shown that earlier tPA administration is associated with better outcome.[4] Although advanced age and

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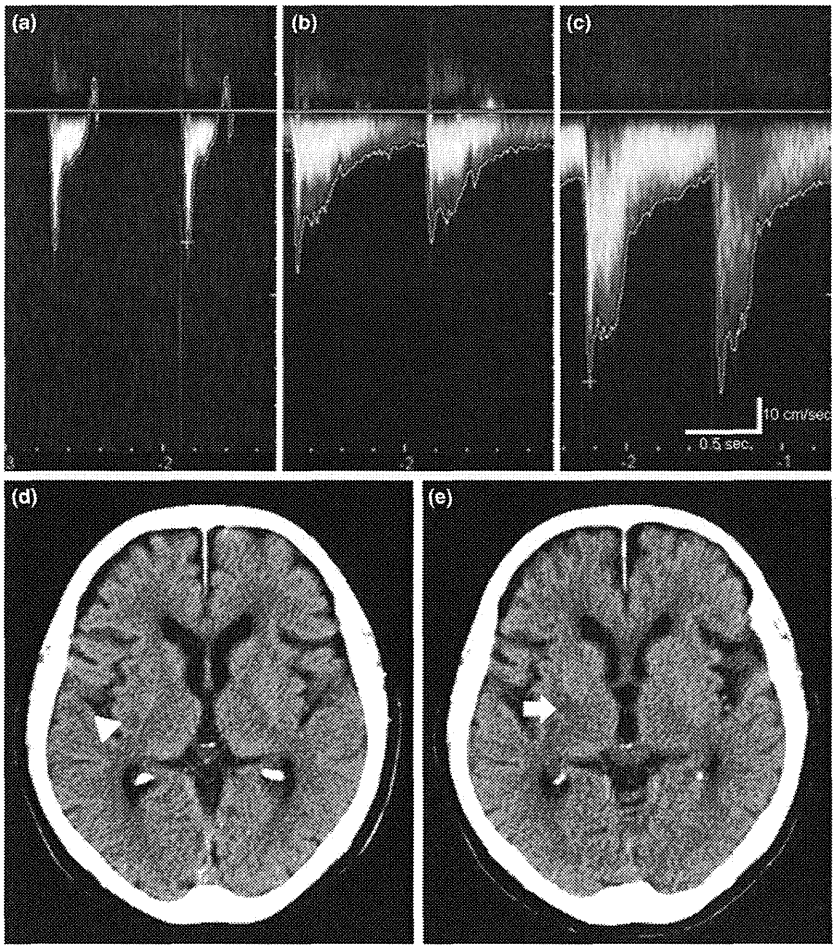

Figure 1 Pulse Doppler findings of the right internal carotid artery. (a) The absence of end diastolic flow on admission. (b) Appearance of end diastolic flow 30 min after starting intravenous thrombolysis. (c) Normalization of blood flow velocity 24 h after starting intravenous thrombolysis; computed tomography of the head. (d) An ambiguous finding of right putaminal hypodensity is shown by an arrowhead shortly after recurrent ischemic stroke. (e) A hypodense area is shown by an arrow in the right putamen on hospital day 14.

ICA occlusion are independent predictors of poor outcome in IS patients receiving tPA,[5] ultra-early onset to treatment time might have contributed to her favorable outcome.

Previous IS within 3 months is a contraindication for intravenous thrombolysis in patients with IS because of the risk of symptomatic intracerebral hemorrhage.[6] However, recent studies of thrombolytic therapy for IS patients with prior TIA compared with no prior TIA have shown that the rate of hemorrhagic complications does not increase and functional outcomes are not influenced.[7,8] We believe that admission of TIA patients to the stroke care unit allows close observation and timely tPA administration, resulting in improved clinical outcomes.

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Etiological mechanisms of isolated pontine infarcts based on arterial territory involvement

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ABSTRACT

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

1. Introduction

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

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

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

2. Methods

2.1. Patient selection and evaluation

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

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

2.2. MRI methods and analysis

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

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

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

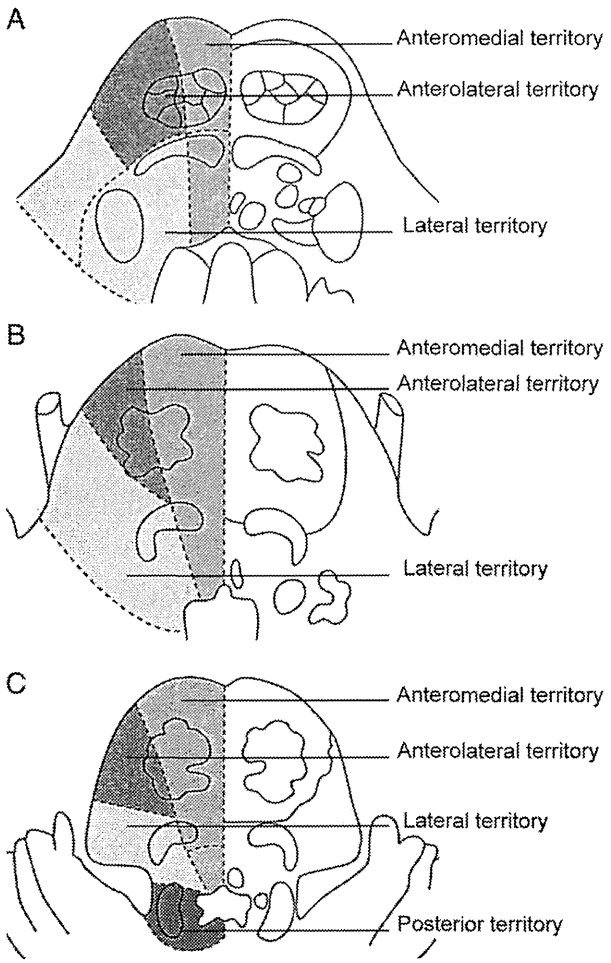

Fig. 1. Vascular perfusion territories of the pons (modified from Tatu L. et al. [8]). A: Lower pons. B: Middle pons. C: Upper pons.

2.3. Clinical characteristics

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

2.4. Statistical analysis

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

3. Results

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

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

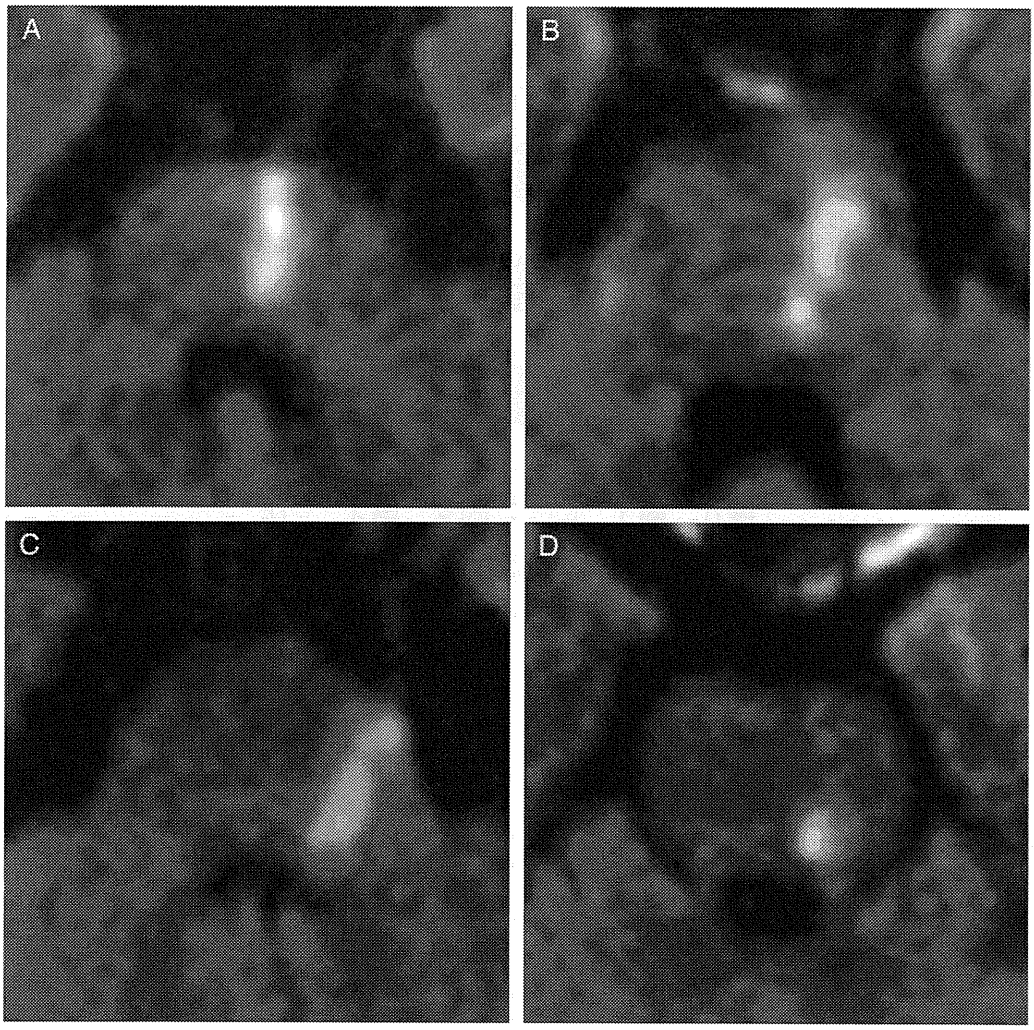

Fig. 2. Pontine infarct locations based on DWI. A: anteromedial pontine infarct. B: anterolateral pontine infarct. C: lateral pontine infarct. D: posterior pontine infarct.

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

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

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

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

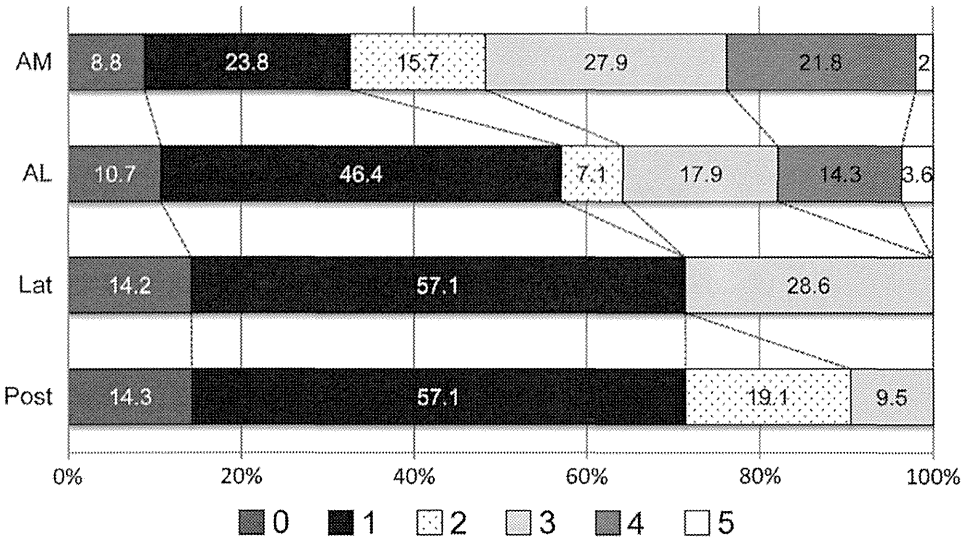

Fig. 3. Modified Rankin Scale score at hospital discharge in patients with isolated pontine infarcts at the four different locations.

4. Discussion

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

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

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

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

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

AM indicates anteromedial; AL, anterolateral; Lat, lateral; Post, posterior; LP, lateral plus posterior; OR, odds ratio; CI, confidential interval; SD, standard deviation.
[a] OR in AL compared with AM.
[b] Average or number of cases was put in bracket; the former corresponding to lateral group, the latter to posterior group.
[c] OR in LP compared with AM.
[d] OR of ages was estimated for a change of 10 years in the age variable.

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

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

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

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

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

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

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

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Disclosure of conflict of interest

None.

Author contribution statement

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

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Stroke and cerebrovascular diseases in patients with chronic kidney disease

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Chronic kidney disease, defined as a reduced glomerular filtration rate or increased urinary albumin excretion, is recognised as a rapidly growing global health burden, and increasing evidence suggests that it contributes to the risk and severity of cerebrovascular diseases. In particular, chronic kidney disease is an established risk factor for stroke and is also strongly associated with subclinical cerebrovascular abnormalities and cognitive impairment, partly because it shares several traditional and non-traditional risk factors, and sometimes uraemia-related and dialysis-related factors, with cerebrovascular diseases. The effect of chronic kidney disease on incident stroke differs among regions and races and is greater in Asian than in non-Asian people. Chronic kidney disease seems to be predictive of severe neurological deficits and poor vital and functional outcomes after both ischaemic and haemorrhagic strokes, which is partly due to the limitations of pharmacotherapies, including limited use and effects of novel oral anticoagulants, other antithrombotic treatments, and reperfusion treatment for hyperacute ischaemic stroke. In view of the strong two-way association between stroke and kidney disease, the pathophysiological interactions between the brain and kidney should be the subject of intensive study.

Introduction

Over the past decade, evidence has grown on the occurrence of stroke and cerebrovascular diseases in patients with chronic kidney disease. Chronic kidney disease is chiefly defined by a reduction in the estimated glomerular filtration rate (eGFR; stages 1 and 2: eGFR normal or mildly reduced [100–60 mL/min per 1·73 m²] with other evidence of kidney disease; stage 3: 59–30 mL/min per 1·73 m²; stages 4 and 5: <30 mL/min per 1·73 m²) or the presence of protein in the urine (proteinuria).[1] The prevalence of chronic kidney disease has been estimated to be 8–16% of the population in many countries worldwide.[2] Beyond the original meaning of chronic kidney disease as a high-risk state for future dialysis, the disease is now recognised as a substantial and rapidly growing global health burden, mainly because it is an established risk factor for cardiovascular disease.[3] Stroke has a strong two-way relation with chronic kidney disease, and the pathophysiological interactions between the brain and kidney—the cerebrorenal interaction—should be as intensely studied as the cardiorenal interaction has been.[4,5] Practically, many vascular neurologists have taken an interest in the renal function of patients since the advent of novel oral anticoagulants, because the activity of these drugs is greatly affected by renal function.[6]

In this Review, we describe the present status of research on the effect of kidney impairment on stroke and other cerebrovascular diseases. We answer seven essential questions to describe the precise nature of the relation between kidney impairment and stroke and cerebrovascular diseases and to provide insights for both clinical and public health specialties.

Is there an increased risk of stroke in patients with chronic kidney disease?

Chronic kidney disease is prevalent in patients with stroke. Figure 1 shows the prevalence of eGFR below 60 mL/min per 1·73 m² in both the general population and in patients with acute stroke. Prevalence varied from 20% to 35% in patients with acute ischaemic stroke[5,10–14] and from 20% to 46% in patients with acute intracerebral haemorrhage (ICH),[5,10,15,16] although creatinine concentrations during acute stroke are increased by acute stroke damage. This prevalence was higher than that in the general population (4–11%) and was similar to that in the general population aged 70 years or older (19–38%).[7–9] This comparison cannot give us a conclusive answer about whether a high prevalence of chronic kidney disease in patients with stroke suggests a causative relation between stroke and chronic kidney disease or whether it is simply due to the fact that stroke and chronic kidney disease share traditional cardiovascular risk factors, including ageing.

There is conflicting epidemiological evidence about whether low eGFR is a risk factor for stroke independent of traditional cardiovascular risk factors.[17–20] In a pooled analysis[19] of 22 634 participants from community-based longitudinal studies including the Atherosclerosis Risk in Communities study, Cardiovascular Health Study, Framingham Heart Study, and Framingham Offspring Study, individuals with an eGFR below 60 mL/min per 1·73 m² had a higher incidence of stroke (10·3 events per 1000 person-years) than those with an eGFR of 60 mL/min per 1·73 m² or higher (3·4 events per 1000 person-years); however, this excess risk of stroke with a lower eGFR was not statistically significant after adjusting for traditional cardiovascular risk factors (hazard ratio [HR] 1·17, 95% CI 0·95–1·44). Conversely, the multivariate-adjusted analysis in individuals with pre-existing cardiovascular disease showed that an eGFR below 60 mL/min per 1·73 m² was associated with a 1·30 times (95% CI 1·04–1·63) increased risk for stroke. Likewise, in a pooled analysis of 30 657 individual participant data from ten community-based cohort studies in Japan, the age-adjusted and sex-adjusted HRs for the

development of stroke increased gradually with lower eGFR: HR 2·06 (95% CI 1·51–2·81) in individuals with an eGFR below 60 mL/min per 1·73 m² compared with those with an eGFR of 90 mL/min per 1·73 m² or higher.[20] Again, the magnitude of the effect of lower eGFR on the risk of stroke was attenuated by about 30%, so that the association did not reach conventional levels of significance (HR 1·41, 95% CI 0·99–2·00 for eGFRs below 60 mL/min per 1·73 m²) after adjusting for traditional risk factors.

However, these non-significant associations between lower eGFR and stroke risk in the multivariate-adjusted analysis are thought to arise from insufficient statistical power. Findings from a meta-analysis of 21 articles derived from 33 prospective studies among 284 672 people experiencing 7863 stroke events,[21] in which multivariate-adjusted relative risks were pooled, suggested that the risk of incident stroke increased by 43% (95% CI 31–57) in patients with an eGFR below 60 mL/min per 1·73 m² (figure 2). Lower eGFR was a risk factor for both ischaemic and haemorrhagic stroke. Additionally, 11 of these 33 studies reported both age-adjusted and sex-adjusted estimates and risk estimates adjusted for other known cardiovascular risk factors. In the sensitivity analysis using this subset of data, the

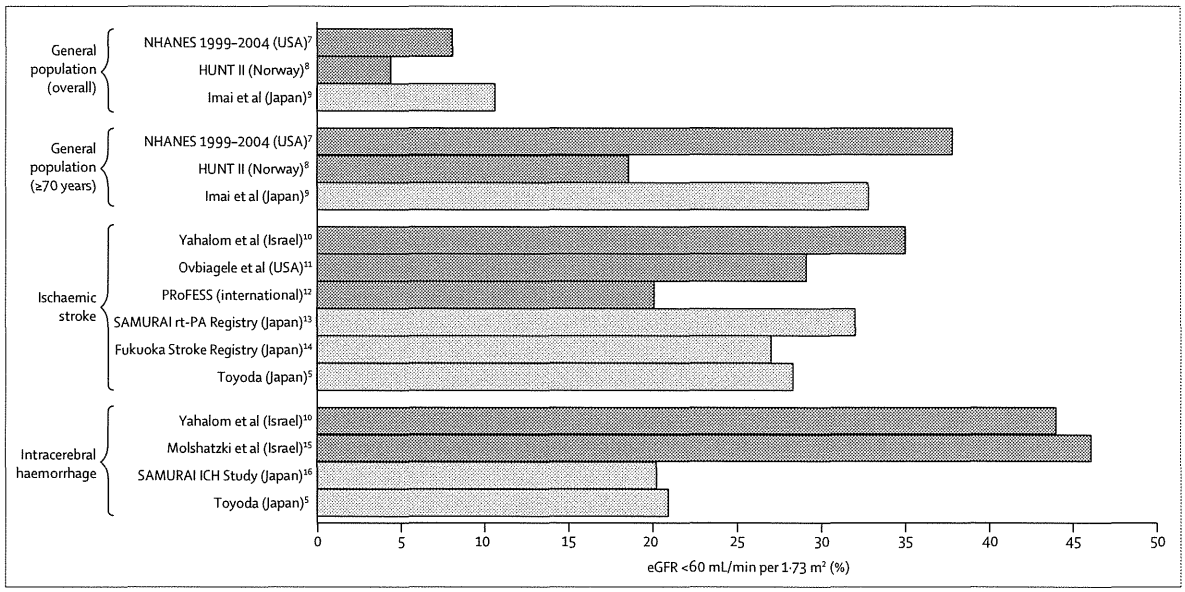

Figure 1: **Prevalence of estimated glomerular filtration rate less than 60 mL/min per 1·73 m² in the general population and in patients with stroke**
Light green bars show data from Japanese participants. Note that eGFR in patients with stroke was measured during the acute stage of stroke and, therefore, might have been affected by stroke-related damage. eGFR=estimated glomerular filtration rate. HUNT=Health Survey of Nord-Trondelag County. NHANES=National Health and Nutrition Examination Survey. PRoFESS=Prevention Regimen for Effectively Avoiding Second Strokes. rt-PA=recombinant tissue plasminogen activator. SAMURAI=Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement.

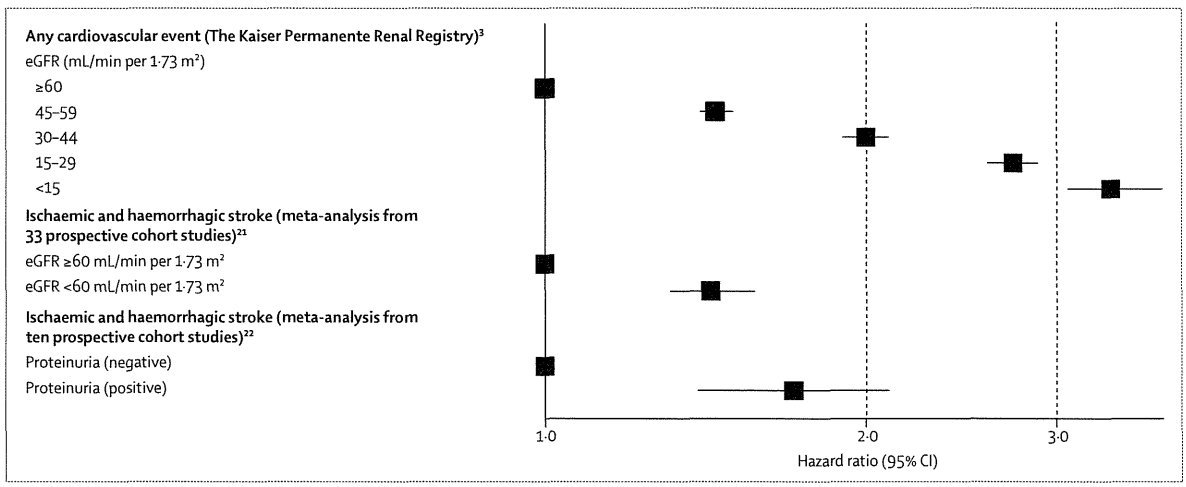

Figure 2: **The association of reduced estimated glomerular filtration rate or proteinuria with the risk of any cardiovascular event or stroke**
Hazard ratios are adjusted for cardiovascular risk factors. eGFR=estimated glomerular filtration rate.

age-adjusted and sex-adjusted summary estimate was 1·64 (95% CI 1·45–1·85), which after further adjustment for other cardiovascular risk factors was reduced to 1·45 (95% 1·26–1·68). The effect of eGFR below 60 mL/min per 1·73 m² on incident stroke was greater in Asian people (risk ratio 1·96, 95% CI 1·73–2·23) than in non-Asian people (1·26, 1·16–1·35). Since hypertension is generally more common and more severe in Asian people than in non-Asian people and is a major risk factor for both chronic kidney disease and stroke,[23] stroke seems to be a greater burden for Asian patients with chronic kidney disease.

Patients with proteinuria, another component of chronic kidney disease, also had a 71% (95% CI 39–110) greater risk of stroke compared with those without proteinuria in a meta-analysis of ten prospective cohort studies involving 140 231 people who experienced 3266 stroke events.[22] The effect of proteinuria on incident stroke seems to vary according to race. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study involving 25 310 community-dwelling participants older than 44 years,[24] higher urinary albumin-to-creatinine ratio was associated with stroke risk independently of traditional risk factors and eGFRs among black participants, and the association was slight among white participants. The association between reduced eGFR and stroke was attenuated after adjusting for albumin-to-creatinine ratio.

These findings not only provide evidence for major involvement of an accumulation of traditional cardiovascular risk factors, but they also raise the possibility that additional novel risk factors play a part in the excess risk of stroke among individuals with low eGFR.[25]

What mechanisms underlie cerebrorenal interactions?

Kidney disease and stroke have common traditional cardiovascular risk factors, such as ageing, diabetes, hypertension, dyslipidaemia, obesity, and smoking;[25] in other words, both the kidney and brain are target organs of arteriosclerotic insults. However, these factors do not seem to be sufficient to capture the extent of the risk for cardiovascular and cerebrovascular diseases in patients with chronic kidney disease. Findings from large-scale meta-analyses show that chronic kidney disease is a significant risk factor for stroke, independent of known cardiovascular risk factors.[21,22] This finding might be due, in part, to the fact that these analyses did not account for the duration of exposure to risk factors and their severity, for which impaired kidney function seems to be an indicator. Novel non-traditional risk factors—namely chronic inflammation, oxidative stress, asymmetric dimethylarginine, sympathetic nerve overactivity, thrombogenic factors, and hyperhomocysteinaemia—also contribute to the excess risk of cerebrovascular disease in patients with chronic kidney disease by triggering vascular injury and endothelial dysfunction. For example, increased concentrations of inflammatory mediators are attributed to increased oxidative stress, and asymmetric dimethylarginine inhibits generation of nitric oxide, leading to endothelial dysfunction and platelet aggregation (figure 3).[26–31] Furthermore, since the influence of uraemia-related factors, such as uraemic toxins, sodium and water retention, anaemia and malnutrition, abnormal calcium and phosphate metabolism, and hyperparathyroidism, becomes more apparent as chronic kidney disease progresses, the risk of cerebrovascular disease is amplified among patients with severe chronic kidney disease. Recently, Klotho protein, which is predominantly expressed in the distal tubule of the kidney, has gained attention as a regulator of cardiovascular disease.[30,31] Klotho serves as a coreceptor for fibroblast growth factor 23, and both proteins contribute to calcium and phosphorus metabolism and maintenance of cell function of endothelium and vascular smooth muscle. Therefore, decreased Klotho protein expression as chronic kidney disease progresses possibly leads to vascular calcification and endothelial dysfunction and might contribute to stroke (figure 4).[30,31]

The kidney and brain share unique susceptibilities to vascular injury since the vasoregulation of the microvasculatures of the two organs is similar anatomically and functionally.[32] Both organs share a low vascular resistance system, allowing continuous high-volume perfusion, and traditional risk factors for vascular injury including hypertension and diabetes.[33] In particular, small-vessel diseases and white matter lesions in the brain are mediated by endothelial dysfunction, ischaemic arteriosclerosis, low perfusion, neurovascular coupling,

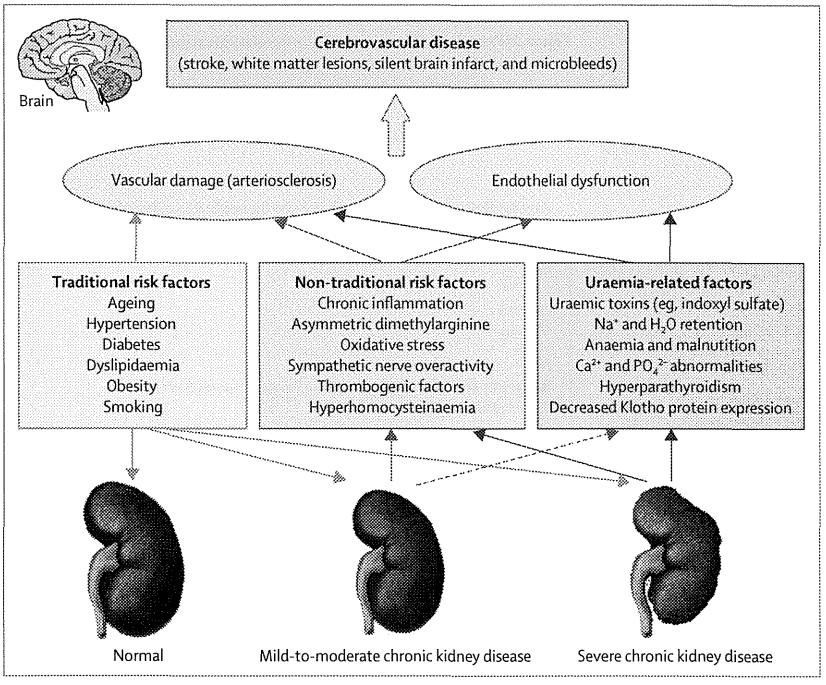

Figure 3: **Traditional and non-traditional risk factors for stroke and kidney disease**

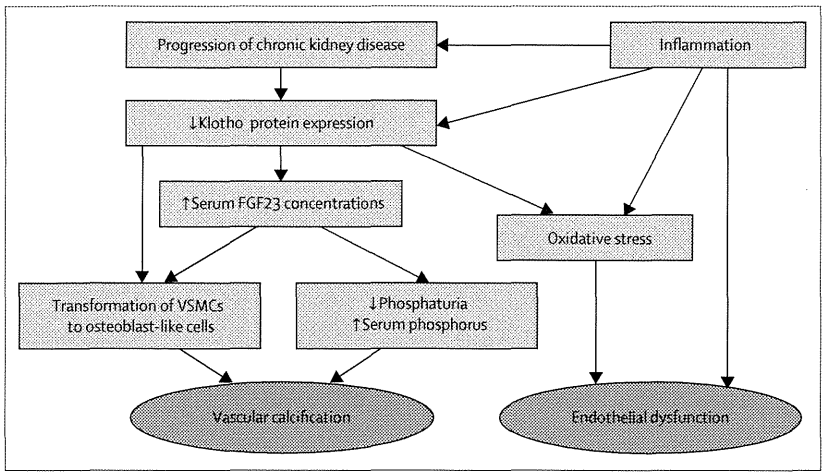

Figure 4: **Effect of Klotho protein on vascular damage in patients with chronic kidney disease**
FGF23=fibroblast growth factor 23. VSMC=vascular smooth muscle cell.

and diffuse blood–brain barrier disruption.[34,35] Kidney impairment is characterised by glomerular endothelial dysfunction and lipohyalinosis, both of which are features of small-artery diseases.[36] Therefore, kidney impairment seems to serve as a predictive marker for the presence and severity of small-vessel diseases and white matter lesions.[37] These tiny brain diseases are frequently associated with silent brain infarcts and cognitive impairments, which are described in the next two sections.

How is chronic kidney disease associated with subclinical cerebral abnormalities?

Findings from several population-based, cross-sectional studies showed that individuals with a lower eGFR had a greater volume of white matter lesions and an increased prevalence of silent brain infarcts on MRI.[38–41] In the Northern Manhattan Study,[38] in 615 stroke-free participants, an eGFR of 15–60 mL/min per 1·73 m² was associated with an increased log-transformed volume of white matter lesions (β 0·322, 95% CI 0·080–0·564) after adjusting for cardiovascular risk factors. The Rotterdam Scan Study[39] of 484 elderly participants (60–90 years of age) showed that those with lower eGFR had a smaller deep white matter volume (difference in standardised volume per 1 SD decrement −0·15, 95% CI −0·26 to −0·04) and greater volume of white matter lesions (difference per 1 SD decrement 0·14, 95% CI 0·03 to 0·25). Additional adjustment for cardiovascular risk factors yielded similar findings.

Likewise, silent brain infarcts are common in individuals with chronic kidney disease. In the Rotterdam Scan Study,[39] lower eGFR also seemed to confer a higher prevalence of silent brain infarcts, although this finding was not statistically significant (age-adjusted and sex-adjusted prevalence odds ratio [OR] per 1 SD decrease in eGFR 1·11, 95% CI 0·81–1·51). In a cross-sectional survey done among elderly adults in the Cardiovascular Health Study, in whom kidney function was assessed by 1/cystatin C concentration,[40] there was a negative linear association between 1/cystatin C and the prevalence of silent brain infarcts (multivariate-adjusted OR per 1 SD decrement 1·20, 95% CI 1·09–1·32). Findings from hospital-based studies involving patients with chronic kidney disease also suggested that lower eGFR was significantly associated with silent brain infarcts and that patients with more advanced stages of chronic kidney disease had a higher prevalence of these infarcts.[42,43] These studies showed a significant association between cerebral small-vessel diseases (white matter lesion and silent brain infarcts) and impaired kidney function, suggesting that moderate-to-severe kidney disease is a possible determinant of cerebrovascular small-vessel diseases or a marker of microangiopathy.

Cerebral microbleeds are also strongly associated with small-vessel diseases. Of 162 patients with chronic kidney disease stages 1–5 not on dialysis who underwent brain MRI,[44] 35 (22%) had cerebral microbleeds. In this cohort, eGFR was inversely associated with the presence of cerebral microbleeds, independent of sex, age, and diastolic blood pressure (OR 0·956 per 1 mL/min increase, 95% CI 0·926–0·988). Cerebral microbleeds were more common in patients with ischaemic or haemorrhagic strokes than in people without stroke. In 236 consecutive inpatients who developed acute ischaemic stroke or transient ischaemic attack, proteinuria was independently associated with both frequency and number of cerebral microbleeds.[45] Similar independent associations were reported in a cohort of predominantly black patients with recent ICH who were registered in the Differences in the Imaging of Primary Haemorrhage based on Ethnicity or Race (DECIPHER) study.[46]

Carotid atherosclerosis is both a predictor of future cardiovascular diseases and a direct embolic source to the brain. Findings from cross-sectional studies of the general population have shown an inverse association of intima-media thickness of the carotid artery with renal function.[47–49] The association seems to be stronger in Asian than in white populations,[50,51] and is also stronger in patient cohorts than in healthy populations.[52–56] The latter finding suggests that the effect of chronic kidney disease on carotid atherosclerosis is clearly stronger in patient cohorts than in the general population.[57] Figure 5 shows the incidence of cardiovascular disease and the prevalence of carotid artery stenosis according to blood pressure category as defined by the European Society of Hypertension and European Society of Cardiology 2007 criteria[60] in participants with and without chronic kidney disease from two reports from the Suita Study,[58,59] an epidemiological study involving Japanese urban residents. In the first report,[58] which included 5494 participants without stroke or myocardial infarction, patients without chronic kidney disease who had normal blood pressure, high-to-normal blood pressure, or those who were hypertensive had increased

risks of cardiovascular disease, including stroke, compared with participants without chronic kidney disease who had optimum blood pressure. However, the effect of each blood pressure category on cardiovascular disease and stroke was more evident in men with chronic kidney disease than in men without. The HR for the association between a 10 mm Hg increase of systolic blood pressure and the risk of cardiovascular disease in men without chronic kidney disease was 1·16 (95% CI 1·09–1·24) and in men with chronic kidney disease it was 1·33 (95% CI 1·15–1·53). In the second report,[59] 3466 individuals without stroke or myocardial infarction underwent a carotid ultrasound examination at baseline. Although the association between chronic kidney disease and carotid artery stenosis was slight, chronic kidney disease was independently associated with stenosis in patients with hypertension (adjusted OR 3·16, 95% CI 2·05–4·88 in those with chronic kidney disease and hypertension compared with those without chronic kidney disease and with optimum blood pressure).

Does chronic kidney disease affect cognitive function?

Dementia and mild cognitive impairment have become as prevalent as stroke, and they are substantial health problems worldwide.[61] Stroke and subclinical cerebral abnormalities are associated with cognitive dysfunction, and chronic kidney disease is associated with these disorders. Accordingly, chronic kidney disease also affects cognitive function.[62–64]

In the REGARDS study,[65] eGFR below 60 mL/min per 1·73 m² (OR 1·23, 95% CI 1·06–1·43), and each 10 mL/min per 1·73 m² decrease of eGFR (1·11, 1·04–1·19), was independently associated with a higher risk of cognitive impairment.[65] Findings from smaller community-based cross-sectional studies also suggested that chronic kidney disease is related to moderate deficits in several cognitive abilities.[66–69]

But what is the association between renal dysfunction and longitudinal cognitive change? In 590 participants in the Maine-Syracuse Longitudinal Study,[70] decline in eGFR over 4–5 years of follow-up, but not the baseline level, was associated with a change in cognitive performance for global cognitive ability, verbal episodic memory, and abstract reasoning. Similarly, in the 7839 participants in the 3C Study,[71] eGFR decline for more than 4 years, but not baseline eGFR, was associated with a decrease in global cognition assessed by the Mini-Mental State Examination. Cognitive impairment is a substantial problem for patients with end-stage kidney disease: an estimated 70% of haemodialysis patients older than 55 years show moderate-to-severe cognitive impairment,[72] with a similar prevalence in patients with peritoneal dialysis.[73] However, the cognitive deficit and impairment begin before the transition to end-stage kidney disease.[64]

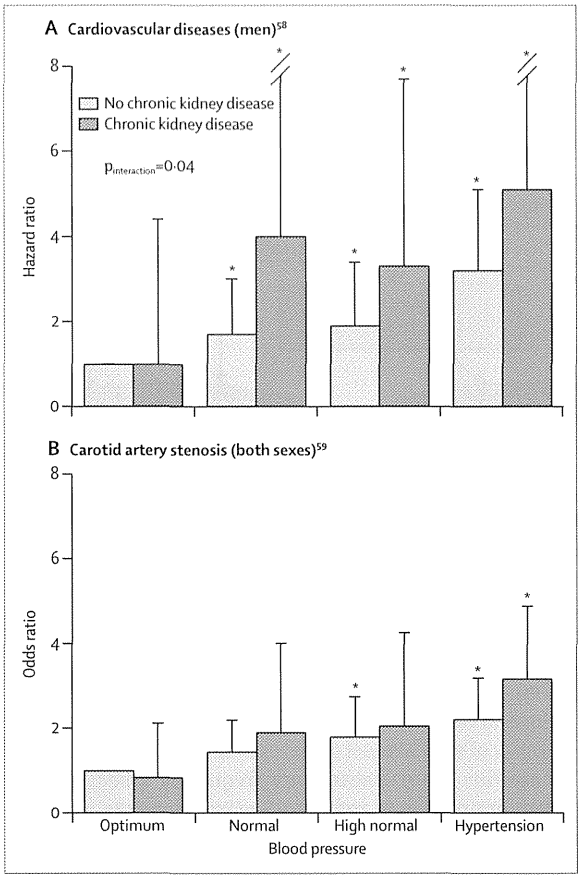

Figure 5: **The association between blood pressure and the effect of chronic kidney disease on clinical and subclinical cardiovascular diseases**
The combination of chronic kidney disease and blood pressure categories on (A) multivariate-adjusted hazard ratios for cardiovascular disease (men) and (B) multivariate-adjusted odds ratios for carotid artery stenosis (both sexes). Data from the Suita Study.[58,59] *p<0·05 versus optimum blood pressure with no chronic kidney disease.

Do patients with chronic kidney disease have more severe strokes than those without?

Chronic kidney disease is predictive of stroke, subclinical cerebrovascular abnormalities, and cognitive impairment, but is stroke in patients with chronic kidney disease more severe than stroke in those without chronic kidney disease?

As far as we know, the report from the Fukuoka Stroke Registry[14] is the largest multicentre, cross-sectional study so far, involving 3778 patients with first-ever ischaemic stroke, of whom 1320 (35%) had chronic kidney disease.[14] After adjustment for potential confounding factors, including initial stroke severity, patients with chronic kidney disease had a 49% (95% CI 17–89) greater risk of neurological deterioration during their hospital stay, defined as at least a 2-point increase in the National Institutes of Health (NIH) Stroke Scale score; a 138% (95% CI 61–257) greater risk of in-hospital mortality; and a 25% (95% CI 5–48) greater risk of a Modified Rankin Scale (mRS) score of 2 or more at discharge than patients without chronic kidney disease. In another study from

the Fukuoka Stroke Registry,[74] there was a 73% (95% CI 3–190) greater risk of recurrence of non-cardioembolic stroke in patients with chronic kidney disease than in those without.[74] Most of the smaller studies clarified the positive association of chronic kidney disease with severe neurological deficits and poor clinical outcome,[10,11,75–77] including 1-year and 10-year mortalities after stroke.[10,76] In a post-hoc analysis of the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial[12] of 18 666 patients with recent ischaemic stroke, of whom 3630 (19%) had an eGFR below 60 mL/min per 1·73 m², patients with reduced eGFR had a 16% (95% CI 4–31) greater risk of recurrent stroke after multivariate adjustment for confounders. In our study of 474 stroke survivors,[78] albuminuria was an independent predictor of ischaemic stroke recurrence. Findings from the China National Stroke Registry[79] showed the association between different eGFRs and clinical outcomes in 4836 patients with diabetes mellitus who were registered within 14 days of stroke or transient ischaemic attack; eGFR below 45 mL/min per 1·73 m² was independently associated with risk of all-cause death, recurrent stroke, the combined endpoint of stroke or death, and stroke disability in patients with overall stroke or transient ischaemic attack and those with ischaemic stroke or transient ischaemic attack.

What are the mechanisms for poorer stroke outcomes in patients with chronic kidney disease? The traditional and non-traditional risk factors listed in figure 3 can be triggers for large infarcts with severe clinical symptoms and a tendency to stroke progression. Additionally, proteinuria and albuminuria are associated with high levels of inflammatory cytokines and oxidative stress,[80,81] potentially causing excessive vascular damage at stroke onset. Albuminuria is also predictive of haemorrhagic transformation of infarcts.[82,83] In some studies, proteinuria showed a much stronger association with unfavourable outcomes than reduced eGFR as a component of chronic kidney disease.[11,14] In our single-centre observational study[84] involving 712 patients with ischaemic stroke, a high serum creatinine concentration at hospital admission was independently associated with high blood pressure during acute stroke and met the inclusion criteria of the Acute Candesartan Cilexetil Therapy in Stroke Survivors (ACCESS) study; acute high blood pressure is generally related to poorer stroke outcomes. Since chronic kidney disease is a predictor of acute kidney injury, poor vital and functional outcomes in patients with chronic kidney disease might be partly mediated by acute kidney injury.[85,86]

How is the effect of renal dysfunction on ICH mediated? Findings from previous studies showed that renal dysfunction (eGFR below 60 mL/min per 1·73 m², proteinuria, serum creatinine ≥132·6 μmol/L) was associated with a large baseline haematoma volume, a low percentage of hospital discharge to home and a high percentage of discharge to a nursing home, and death or disability at 1 year.[87–89] The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-ICH study,[90–92] a prospective, multicentre, observational study, was undertaken to assess the safety and feasibility of early (within 3 h from onset) systolic blood pressure reduction to lower than 160 mm Hg with intravenous nicardipine in 211 patients with acute spontaneous ICH. In a subanalysis,[16] eGFR below 60 mL/min per 1·73 m² was positively associated with a mRS score of 5–6 (OR 5·87, 95% CI 1·87–19·34) and negatively associated with a score of 0–2 (0·21, 0·07–0·54) at 3 months, after adjustment for known prognostic predictors including the initial NIH Stroke Scale score and haematoma volume. Patients with ICH have a higher chance of receiving intensive antihypertensive treatment than those with ischaemic stroke in the emergency setting. In the Antihypertensive Treatment of Acute Cerebral Haemorrhage (ATACH) study,[93] five (8%) of 60 patients with ICH who were receiving intravenous nicardipine according to the predefined standardised protocol had acute kidney injury, and those patients with acute kidney injury frequently had neurological deterioration and symptomatic haematoma expansion at follow-up.

How does chronic kidney disease affect stroke management?

In terms of the poor stroke outcomes of patients with chronic kidney disease, resistance to and limitations of stroke treatments should be discussed. The panel lists the limitations of pharmacotherapy, endovascular treatment, and surgical carotid revascularisation for patients with stroke and chronic kidney disease.[6,93–104] The dilemma is that patients with chronic kidney disease have both high thromboembolic risk and high bleeding risk, since renal dysfunction is a component of indices for both ischaemia risk prediction and bleeding risk prediction.[105,106] Thus, maintaining the balance of the risk and benefit of antithrombotic treatment in patients with chronic kidney disease is often difficult. Of the various stroke treatments, intravenous thrombolysis with alteplase and anti-coagulation for patients with atrial fibrillation will be used as examples.

Alteplase, the only thrombolytic drug approved for clinical use in patients with stroke worldwide, is metabolised by the liver, and the plasma concentration–time profile of alteplase was not altered in a rat model of bilateral nephrectomy.[107] Therefore, renal dysfunction might not prolong the half-life of alteplase. Nevertheless, patients with chronic kidney disease seem to have worse recovery and higher risk of bleeding complications after thrombolysis than those without chronic kidney disease. Three studies investigated the association between renal dysfunction at admission and unfavourable outcomes after alteplase treatment:[13,108,109] two reported a positive association[13,108] and the other did not show significant association.[109] A meta-analysis was done of these three studies, which involved 344 patients with reduced eGFR

(below 90 mL/min per 1·73 m² in one study[108] and below 60 mL/min per 1·73 m² in the other two[13,109]) and 504 patients without reduced eGFR, after reaching a consensus on the differences in study designs (figure 6).[100] Reduced eGRF was associated with early symptomatic ICH (7·6% in patients with reduced eGFR *vs* 2·4% in those without; OR 3·38, 95% CI 1·60–7·15), high mortality (14·2% *vs* 4·6%; 3·15, 1·82–5·45), and low percentage of patients with a mRS score of 0–2 (45·6% *vs* 53·2%; 0·60, 0·45–0·81) at 3 months[13,108] or at hospital discharge.[109] In addition to the role of chronic kidney disease as a predictor of poor outcome in general stroke, special situations might obstruct the reperfusion phenomenon and worsen outcomes after thrombolysis—ie, hypertensive patients with chronic kidney disease have impaired endothelial release of t-PA, diabetic patients with albuminuria have higher plasminogen activator inhibitor-1 activity than diabetic patients without albuminuria, and plasma concentrations of lipoprotein(a)—a homologue of plasminogen that inhibits plasminogen activation—are raised in patients with renal disease.[13]

Atrial fibrillation is one of the strongest risk factors for stroke. The prevalence of atrial fibrillation in patients with late-stage chronic kidney disease, including end-stage kidney disease, varies from 7% to 27%, and is higher than that in the general population (<10%).[110] In the Danish national registries involving 132 372 patients with non-valvular atrial fibrillation,[95] those with non-end-stage chronic kidney disease or end-stage kidney disease had increased risk of stroke and increased bleeding risk compared with patients with normal renal function. Indeed, renal dysfunction is a key component of the HAS-BLED and HEMORR$_2$HAGES bleeding risk scores for patients with atrial fibrillation who are undergoing anticoagulation.[111,112] Thus, special caution for prevention of bleeding complications is needed for anticoagulation in patients with both chronic kidney disease and atrial fibrillation. There is conflicting evidence for the benefit of stroke prevention from warfarin, especially in patients on dialysis. In the aforementioned Danish national registries,[95] warfarin significantly decreased the risk of stroke and significantly increased the risk of bleeding for patients with either non-end-stage chronic kidney disease or end-stage kidney disease. Furthermore, findings from another study involving 399 patients with late-stage chronic kidney disease,[97] including end-stage kidney disease, showed a decrease in incident stroke with warfarin with an optimum intensity (international normalised ratio 2·0–3·0) regardless of the stage of chronic kidney disease. By contrast, other studies reported that warfarin increased bleeding risk, ischaemic stroke risk, and mortality in patients with atrial fibrillation who were on dialysis.[98,99] Warfarin in patients on dialysis also increases vascular calcification.[98] Thus, routine use of warfarin in patients with end-stage kidney disease is often limited to those at very high risk of stroke and done under close monitoring of international normalised ratio. Although newer oral anticoagulants seem to be safer and more effective for patients with non-valvular atrial fibrillation than warfarin,[6] they are contraindicated for patients with advanced renal dysfunction owing to reduced clearance.

Because chronic kidney disease affects management of stroke, management of chronic kidney disease can also affect stroke risk and severity. Prevention of advancement of chronic kidney disease stages generally decreases stroke risk and attenuates stroke severity. Although management of chronic kidney disease varies according to the underlying nephropathy, risk factor modification, in particular reduction of blood pressure, is common for most patients with chronic kidney

Panel: Limitations in stroke management for patients with chronic kidney disease

Pharmacotherapy in general
- Special dosage considerations.
- Enhanced bleeding complications with antithrombotic treatment.[94,95]

Antiplatelet treatment
- Reduced responsiveness to antiplatelet drugs.[96]

Anticoagulation
- Conflicting evidence for benefit of stroke prevention from warfarin, especially in patients on haemodialysis.[95,97-99]
- Limited use of novel oral anticoagulants in patients with advanced renal impairment.[6]

Thrombolysis
- Poor therapeutic effect of recombinant tissue plasminogen activator.[100]
- Enhanced intracerebral haemorrhage.[100]

Neuroprotective therapy
- Limited use of edaravone (a free radical scavenger approved in Japan) in patients with advanced renal impairment.[101]

Risk factor management
- Risk of acute kidney injury by aggressive blood pressure reduction.[93]

Endovascular treatment
- Limited use of contrast agents.
- Difficulty in catheterisation because of carotid calcification.
- Low rates of freedom from stroke and survival in patients with an estimated glomerular filtration rate below 30 mL/min per 1·73 m².[102]

Carotid endarterectomy
- Increased risk for cardiac and pulmonary morbidities.[103,104]
- High operative mortality in patients with an estimated glomerular filtration rate below 30 mL/min per 1·73 m².[103]

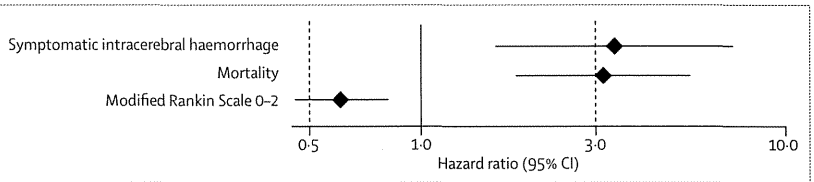

Figure 6: **Meta-analysis of symptomatic intracerebral haemorrhage, mortality, and outcome after intravenous thrombolysis in patients with chronic kidney disease**
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