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Stroke and cerebrovascular diseases in patients with chronic kidney disease

Kazunori Toyoda, Toshiharu Ninomiya

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.

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Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan (K Toyoda MD); **and Center for Cohort Studies, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan** (T Ninomiya MD)

Correspondence to:
Dr Kazunori Toyoda, Department of Cerebrovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Osaka 565–8565, Japan
toyoda@ncvc.go.jp

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 patho-physiological 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 Off-spring 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

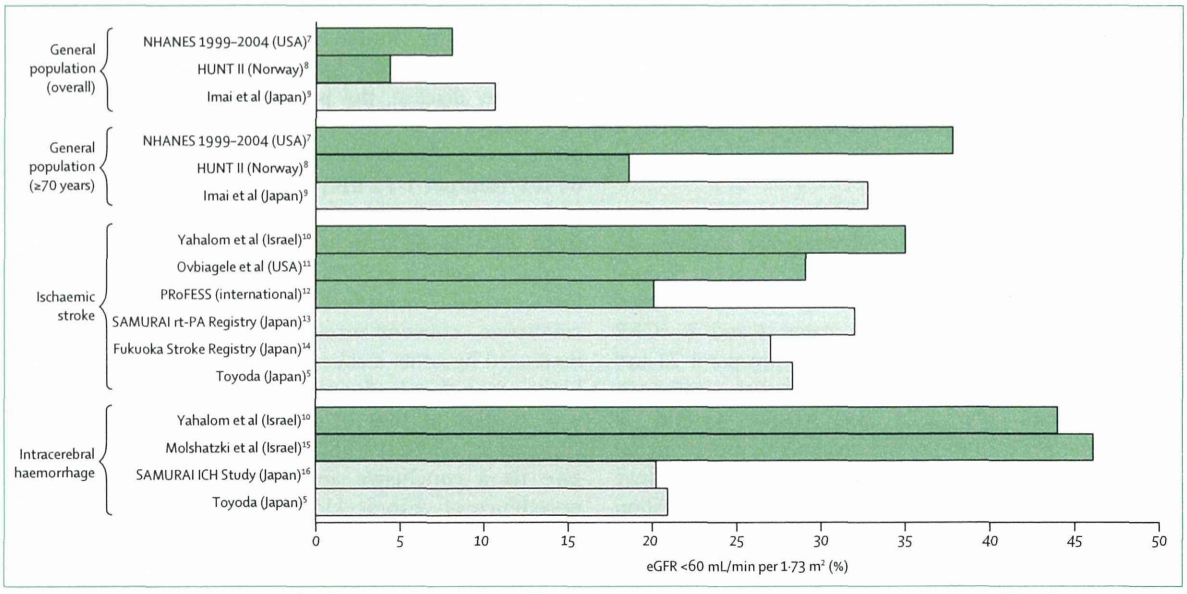

Figure 1: **Prevalence of estimated glomerular filtration rate less than 60 mL/min per 1·73 m² in the general population and in patients with stroke**
Light green bars show data from Japanese participants. Note that eGFR in patients with stroke was measured during the acute stage of stroke and, therefore, 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.

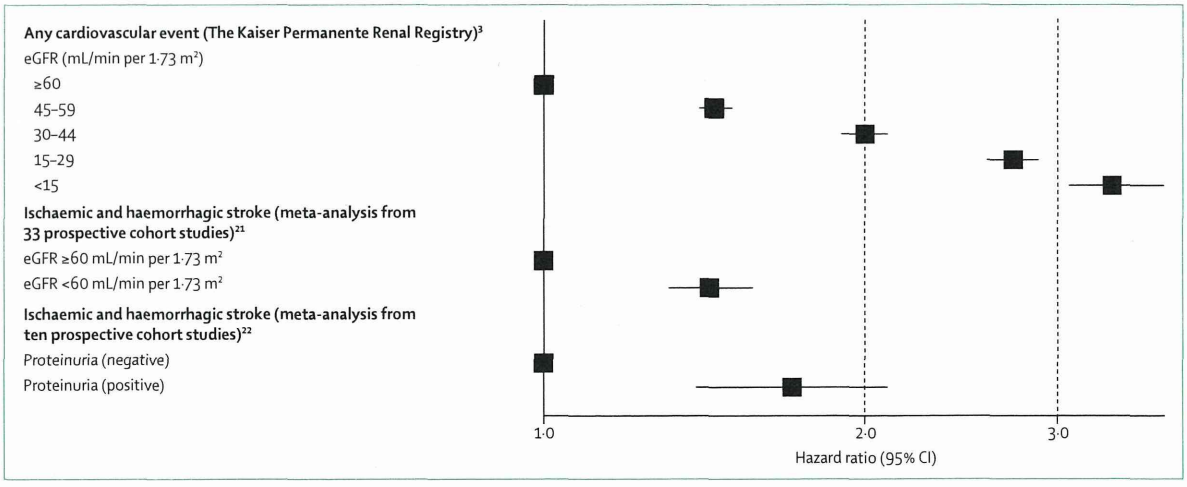

Figure 2: **The association of reduced estimated glomerular filtration rate or proteinuria with the risk of any cardiovascular event or stroke**
Hazard ratios are adjusted for cardiovascular risk factors. eGFR=estimated glomerular filtration rate.

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,

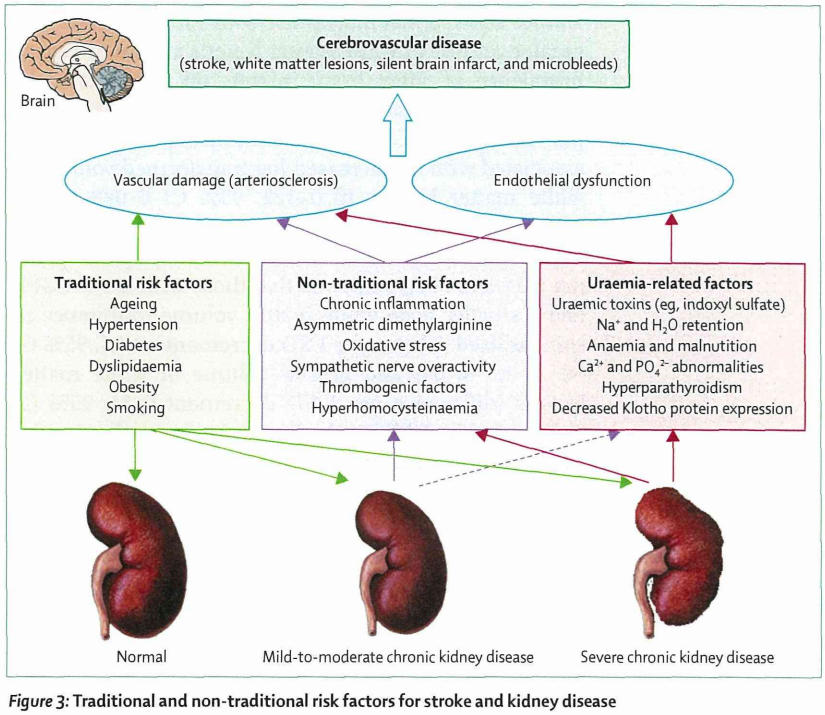

Figure 3: **Traditional and non-traditional risk factors for stroke and kidney disease**

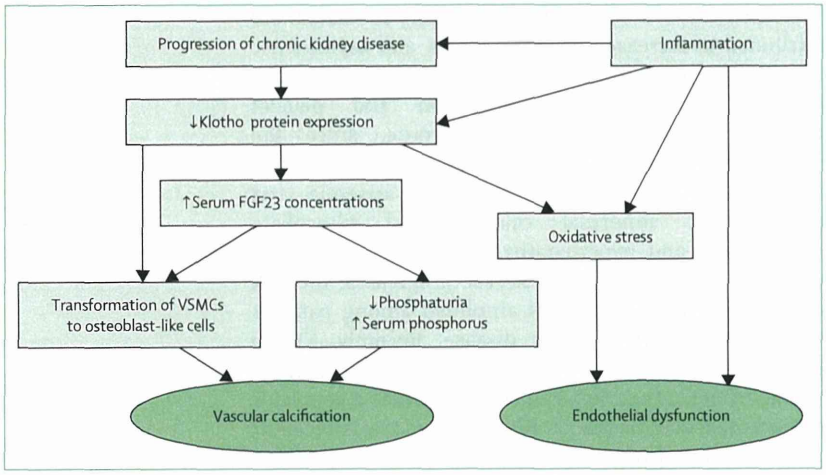

Figure 4: **Effect of Klotho protein on vascular damage in patients with chronic kidney disease**
FGF23=fibroblast growth factor 23. VSMC=vascular smooth muscle cell.

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]

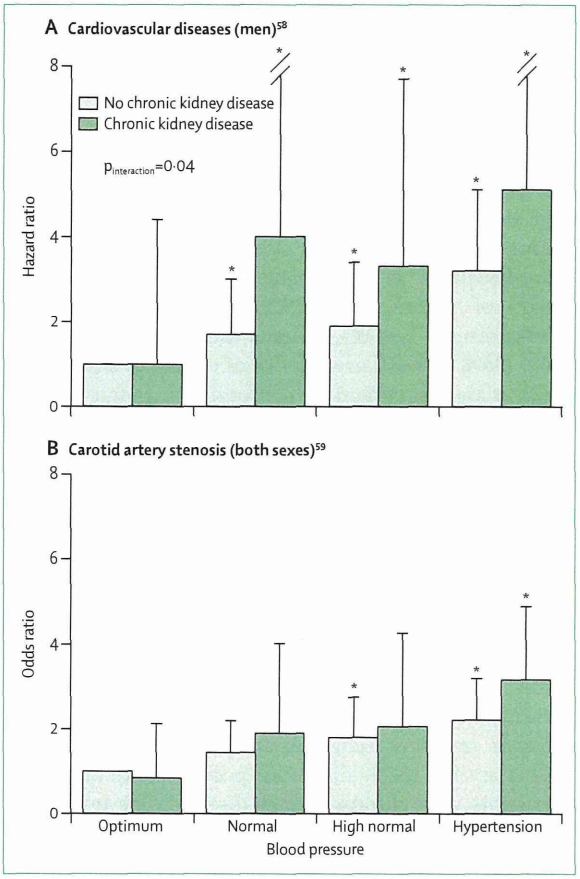

Figure 5: **The association between blood pressure and the effect of chronic kidney disease on clinical and subclinical cardiovascular diseases**
The combination of chronic kidney disease and blood pressure categories on (A) multivariate-adjusted hazard ratios for cardiovascular disease (men) and (B) 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]

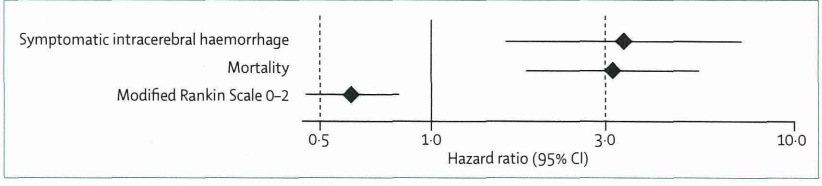

Figure 6: **Meta-analysis of symptomatic intracerebral haemorrhage, mortality, and outcome after intravenous thrombolysis in patients with chronic kidney disease**
Modified with permission from Hirano.[100] © S Kargar AG, Basel.

disease. For these patients, a lower target blood pressure than for patients without chronic kidney disease is generally needed, and initial antihypertensive treatments should include an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to improve kidney outcomes.[113] Strategies for management of chronic kidney disease often depend on the health-care system in individual countries.[2] Living in a country with low socioeconomic status increases the risk of progressive chronic kidney disease.[114] Because renal replacement treatments are costly, care for patients with end-stage kidney disease is often insufficient in developing countries and might further increase stroke risk of patients with kidney disease in such countries.

What is the burden of stroke in patients with end-stage kidney disease?

Stroke is common in patients with end-stage kidney disease, both in those undergoing haemodialysis[115] and those undergoing peritoneal dialysis.[116] The risk of stroke in patients on dialysis is four to ten times higher than that in the general population.[117] One study found that stroke in patients with nephropathy caused by either nephrosclerosis or diabetes mellitus was likely to develop early after starting dialysis, whereas in most patients with chronic glomerulonephritis who had stroke events these occurred more than 36 months after starting dialysis treatment.[118] Supportive findings from a Japanese cohort study of 2977 patients with chronic kidney disease with eGFR of 10–59 mL/min per 1·73 m² showed that patients with chronic glomerulonephritis had a lower brachial-ankle pulse wave velocity—a marker of atherosclerotic disease—than those with diabetic nephropathy or non-chronic glomerulonephritic kidney disease.[119] This finding supports the hypothesis that kidney impairment in combination with other cardiovascular risk factors accelerates atherosclerosis and raises the risk of the development of stroke in the predialysis stages. By contrast, characteristics unique to dialysis, such as drastic haemodynamic change and consequent high variability of blood pressure, dialysate and anticoagulants, vascular access, dialysis amyloidosis, vascular calcification, and years on dialysis, can be triggers of both ischaemic and haemorrhagic strokes.[120,121]

Search strategy and selection criteria

We searched PubMed for articles published in English up to Oct 31, 2013, with the search terms "kidney", "renal", "haemodialysis", "brain", "stroke", "cerebral infarction", "intracerebral haemorrhage", "cerebrovascular", "white matter", "microbleed", "carotid artery", "cognition", and "dementia". Additionally, we searched references from relevant articles and those from a personal library. The final reference list was generated on the basis of originality and relevance to topics covered in this Review.

Acute management of stroke is further restricted in patients with end-stage kidney disease compared with patients with milder chronic kidney disease; for example, by the contraindication of some pharmacotherapies including the newer oral anticoagulants and the difficulty of continuing dialysis in the same physical condition as before when severe neurological deficits remain. Since patients on haemodialysis often develop stroke while at dialysis clinics,[115] good emergent cooperation between dialysis clinics and stroke centres is needed to increase the chance that patients receive hyperacute thrombolysis and thrombectomy. Intravenous thrombolysis is not contraindicated for patients with end-stage kidney disease;[122] however, even thrombolysis experts often have limited experience with this treatment in these patients.[123]

Conclusions and future directions

Our review of the strong associations of chronic kidney disease with stroke and subclinical cerebrovascular diseases shows that the time has come for neurology to meet nephrology. Preventive management strategies for chronic kidney disease and for cerebrovascular diseases have a lot in common. Additionally, chronic kidney disease further increases the risk of cerebrovascular diseases in patients with vascular risk factors. Large clinical trials have generally excluded patients with advanced renal dysfunction because of safety issues, and, therefore, establishment of novel treatments for such patients is often difficult. A practical strategy to expand stroke management in patients with chronic kidney disease might be to expand the indications of existing pharmacotherapies that are limited at present because of their major excretion from the kidney, by developing dosages and intervals of drug administration. Development of drugs with both neuroprotective and nephroprotective effects is also awaited. A thorough understanding of the cerebrorenal interaction is important to minimise the burden of cerebrovascular disease in patients with chronic kidney disease. Attempts to achieve these goals will benefit from collaboration between neurologists and nephrologists.

Contributors

The authors contributed equally to the planning and writing of this Review, KT mainly from a clinical perspective and TN mainly from an epidemiological perspective.

Declaration of interests

We declare no competing interests.

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