	利点	欠点
ビタミンK	血液製剤と比して効果が持続的	効果発現までに6時間程度を要する
新鮮凍結血漿（FFP）		効果時間が短い 必要水分量が多い 解凍が必要 輸血の一般的リスクがある 第Ⅳ因子の濃度が不十分かもしれない
プロトロンビン複合体製剤（PPC）	FFPよりPT-INR是正が早い FFPよりも水分量が少ない 解凍の必要がない	保険適応外 血栓塞栓症のリスク増大
遺伝子組換え活性化第Ⅶ因子製剤（rFⅦa）		使用に関して十分な根拠がない 半減期が短く、反復投与が必要 高価である

表1　ワルファリンの緊急中和手段
（文献2より改変引用）

PCC）は500単位製剤（25mL）に血液500mL中の第Ⅱ、Ⅶ、Ⅸ、X凝固因子が凝縮されており、循環血液量に負荷をかけることはなく、投与後10～15分ほどで効果が発現する。ワルファリン関連大出血を発症した202人に対し、4因子含有プロトロンビン複合体製剤（four-factor prothrombin complex concentrate：4F-PCC）の有効性をFFPと比較した試験[3]では、投与30分後のプロトロンビン時間国際標準比（prothrombin time international normalized ratio：PT-INR）の是正（1.3以下）はFFP（PT-INR値により10～15mL/kg）群で9.6％に対し4F-PCC（PT-INR値により25～50単位/kg）群では62.2％に認められた。しかし、24時間後までの止血効果は、4F-PCC群72.4％およびFFP群65.4％で、同程度であった。「循環器疾患における抗凝固・抗血小板療法に関するガイドライン（2009年改訂版）」「脳卒中治療ガイドライン2009」では、FFPよりもPCCの使用が推奨されている。ただし、現在わが国においてPCCはワルファリンの緊急是正に対する保険適応はなく適応外使用となる。

PCC使用に際して注意すべき点としては、血栓症リスクが上昇することがあげられる。ワルファリン療法中の出血あるいは緊急手術のためにPCCを使用した27試験、計1,032人のメタ解析では、1.4％と高頻度ではないが全身血栓塞栓症リスクが存在した[4]。なお、血液製剤（FFP、PCC）単独投与では低下したPT-INRが12～24時間後に再上昇するため、ビタミンKとともに投与することが推奨される。

遺伝子組換え活性化第Ⅶ因子製剤（recombinant activated factor Ⅶ：rFⅦa）は使用するには十分な科学的根拠はなく、保険適応外で非常に高価である。

脳出血時の具体的中和法

ワルファリン内服中の脳出血において、PT-INRの是正が不十分（PT-INR＞1.35）な場合には3日以内に再出血を起こしやすいことが報告されており[5]、「脳卒中治療ガイドライン2009」では、できる限り速やかにPT-INRを1.35以下に正常化させることが勧められている。

国立循環器病研究センター脳血管内科・脳神経内科では、ワルファリン内服中の脳出血症例に対して、下記の指針で中和を行っている。具体例を示す（図1）。

・PT-INRが1.35以下であれば中和は施行しない。
・PT-INRが1.35超3未満ではPCC（PPSB-HT「ニチヤク」、日本製薬）500単位、PT-INRが3以上ではPCC 1,000単位を静注し、ビタミンK 10～20mgを併用する。10分後にPT-INRを再検し、PT-INRが1.35以上であればPCC 500単位を追加静注する。

ワルファリン中和の課題

前述のようにワルファリンの緊急是正を目的とした場合のPCC使用は保険適応外となるため、患者と患者家族への十分な説明と同意の下に投与するべきである。ワルファリン療法中の急性重度出血あるいは外科手術または介入的処置のために緊急是正に対する

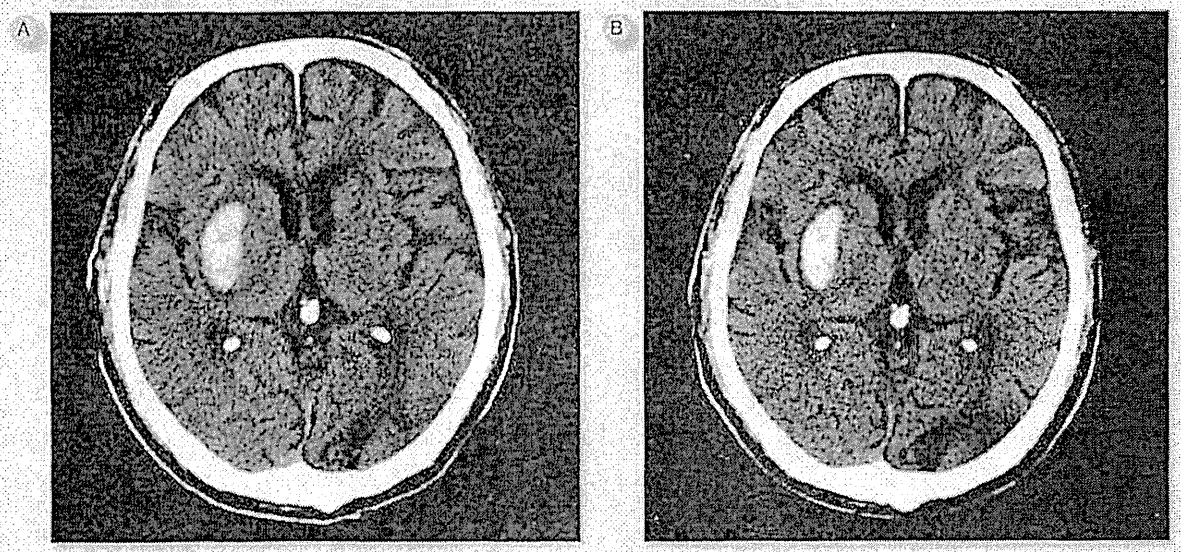

図1　ワルファリン中和の具体例

79歳、男性。発作性心房細動(CHADS2スコア4点、CHA_2DS_2-VAScスコア5点、HAS-BLEDスコア4点)、陳旧性脳梗塞(心原性脳塞栓症)にてワルファリン内服中であった。突然の左上下肢脱力にて、発症1時間15分で当院救急搬送。血圧192/100mmHg、構音障害と左不全片麻痺を認めNIHSS 5点。頭部CT(A)にて右基底出血の診断(推定血腫量7mL)。直ちに降圧を開始。PT-INR 1.82であり、PPSB 500単位とビタミンK 10mgを静注。10分後のPT-INRは1.25と是正された。4時間後の頭部CTにて血腫拡大なし(B)。72時間後よりヘパリン1万単位/日持続静注で抗凝固療法再開し、第5病日よりアピキサバン10mg/日内服に移行した。経過良好にてNIHSS 2点、mRS 2で自宅退院。

PCC(Beriplex®、CSLベーリング)の第Ⅲ相臨床試験が開始されており、今後早期の適応取得が待たれるところである。

NOACs内服中の緊急中和手段(表2)

NOACsに対する緊急中和の現状

現在、NOACsに対して確立された中和手段は存在せず、使用できる特異的中和剤はない。そのため、大出血時に抗凝固作用の十分な是正が行えず、重症化しやすいのではないかという懸念があった。しかし、これまでNOACsがワルファリンと比較して大出血発現後の転帰が不良であるとする報告はない。ダビガトランとワルファリンを比較した5つの第Ⅲ相試験のレビューにおいて、大出血発現後30日以内の死亡率は、ワルファリン群(13.0%)と比較してダビガトラン群(9.1%)で低い傾向にあった[6]。ROCKET-AFのサブ解析において、大出血を発現した際の死亡率は、リバーロキサバン群20.4%、ワルファリン群26.1%で同等であった[7]。頭蓋内出血に限ってみても、発症した際の死亡率に関して、ワルファリン群とダビガトラン群で同等であった[8]。少数例での検討ではあるが、NOACs関連脳出血は、ワルファリン関連脳出血と比較して血腫が小さく、血腫拡大が少なく、転帰が良好であったとの報告がある[9,10]。

とはいうものの、NOACs内服中に重篤な出血をきたした場合には、できる限り速やかに抗凝固作用を是正することが望ましい。そのため、これまで一般的な止血薬の有効性が評価されてきた。動物実験では、PCCがダビガトラン関連脳出血の血腫拡大[11]を、PCC、FFP、rFⅦaがリバーロキサバン関連脳出血の血腫拡大を防いだ[12]との報告がある。健常ボランティア12人での検討では、PCC 50単位/kgはリバーロキサバン投与中の延長したPTを是正したが、ダビガトラン投与中の延長した活性化部分トロンボプラスチン時間activated partial thromboplastin time(activated partial thromboplastin time：APTT)、エカリン凝固時間(ecarin clotting time：

表2　NOACsの緊急是正に対する提言
（文献16より改変引用）

	ダビガトラン	リバーロキサバン	アピキサバン
経口活性炭	有効	有効	有効
血液透析	有効	無効	無効
活性炭血液灌流	有効	有効かもしれない	有効かもしれない
新鮮凍結血漿	無効	無効	無効
活性化第Ⅶ因子製剤	不明	不明	不明
3因子含有プロトロンビン複合体製剤	不明	不明	不明
4因子含有プロトロンビン複合体製剤	有効かもしれない	有効かもしれない	有効かもしれない

ECT)、トロンボテスト(thrombo test：TT)は是正しなかった[10]。健常ボランティアを用いた別の*in vitro*試験において、PCC、活性型プロトロンビン複合体製剤(activated prothrombin complex concentrate：aPCC)およびrF Ⅶaの投与はダビガトランならびにリバーロキサバンの抗凝固作用を是正した[14]。

これらの研究は動物実験であるか、ヒトにおいてはラボデータの是正を目的としており、現在のところヒトにおける臨床上の止血を目的とした研究はない。そのため、NOACs内服中の出血に対する非特異的中和剤の使用に関して十分な科学的根拠があるとはいえず、コンセンサスは得られていない。2011年5月に米国の脳卒中専門医221人を対象として行われたアンケートでは、ダビガトラン関連脳出血に対して抗凝固作用是正を試みると答えたのは73%であり、その方法(複数選択可)はPCC 61%、FFP 53%、rF Ⅶa 24%、血液透析24%、血小板輸血7%と多様であった[15]。2011年12月に行われた北米血栓止血学サミットでまとめられたエキスパートガイダンスにおいて、NOACs内服中の致死的出血や緊急手術前の抗凝固作用是正としてのPCCの使用は、有効性は確立されていないが合理的な選択肢の1つであると提言されている[16]。欧州心臓律動学会(European Heart Rhythm Association：EHRA)のプラクティカルガイドでは、NOACs内服中の生命を脅かす出血に対して、十分な科学的根拠はないとしながらも、PCC 25単位/kg、aPCC 50 IE/kg、rF Ⅶa 90μg/kgの投与を考慮してもよいと提唱されている[17]。

そのほかの抗凝固作用是正手段

NOACの場合、食後の最高血中濃度到達時間(Tmax)が30分～4時間程度なので、最終内服から2～3時間以内の場合は活性炭の投与による吸収抑制が有効である。

ダビガトランについては、最終内服から2～3時間以内、あるいは腎機能障害を有する患者においては緊急血液透析が有効である。一方、リバーロキサバンとアピキサバンは蛋白結合率が高く、血液透析で除去されない[18]。

NOACsに対する特異的中和剤の開発状況

ダビガトランの中和剤として開発されたヒト化抗体フラグメントIdarucizumab(aDabi-Fab/BI655075、ベーリンガーインゲルハイム)は、現在第Ⅲ相試験RE-VERSE ADが欧州にて進行中であり、わが国においても2015年に開始される予定である。Xa阻害薬に関しては、特異的に結合する遺伝子組換え蛋白(Andexanet alfa/PRT4445、Portola Pharmaceuticals)が開発中である。これら特異的中和剤の臨床現場への登場が待たれる。

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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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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

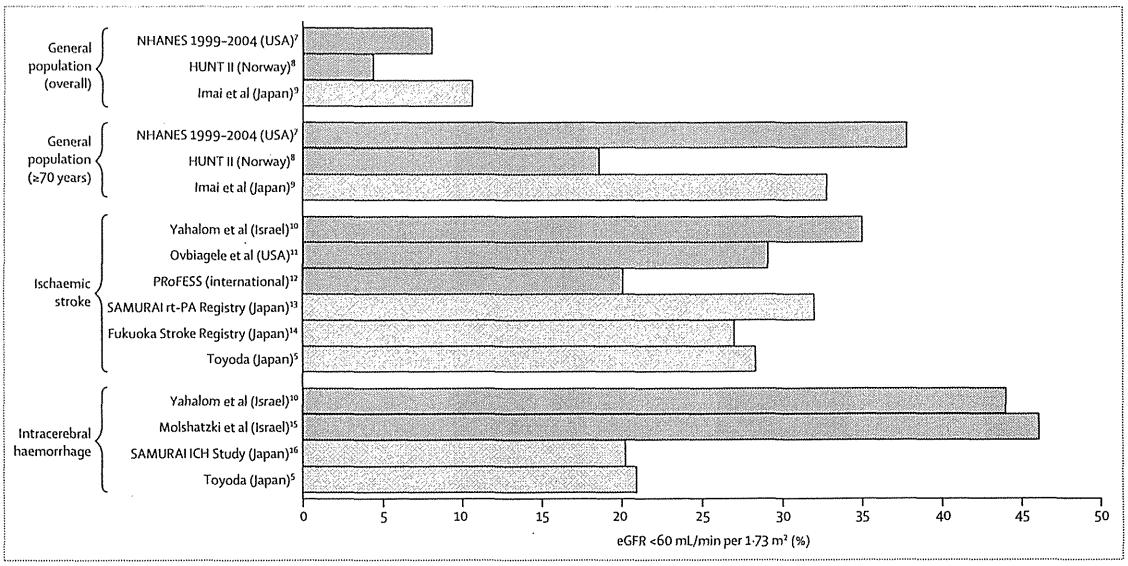

Figure 1: **Prevalence of estimated glomerular filtration rate less than 60 mL/min per 1·73 m² in the general population and in patients with stroke**
Light green bars show data from Japanese participants. Note that eGFR in patients with stroke was measured during the acute stage of stroke and, therefore,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

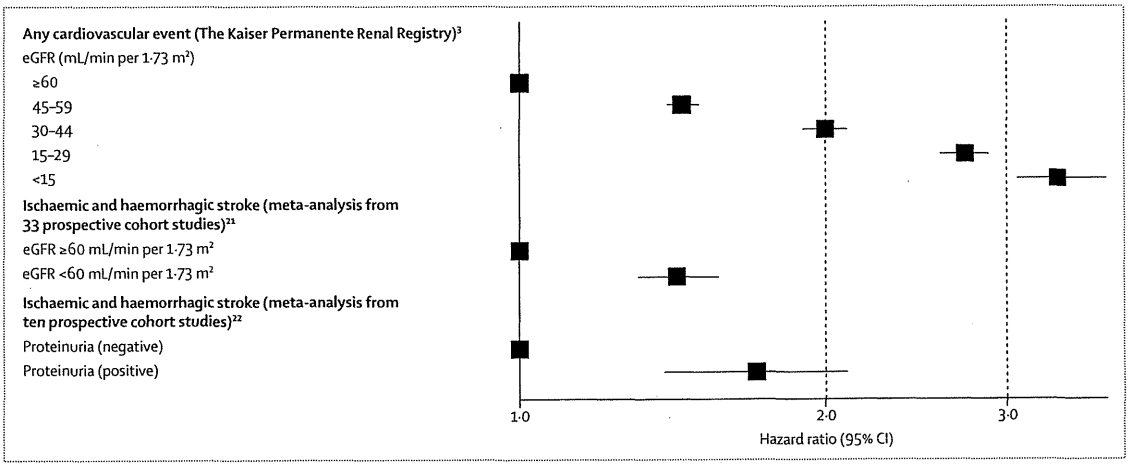

Figure 2: **The association of reduced estimated glomerular filtration rate or proteinuria with the risk of any cardiovascular event or stroke**
Hazard ratios are adjusted for cardiovascular risk factors. eGFR=estimated glomerular filtration rate.

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,

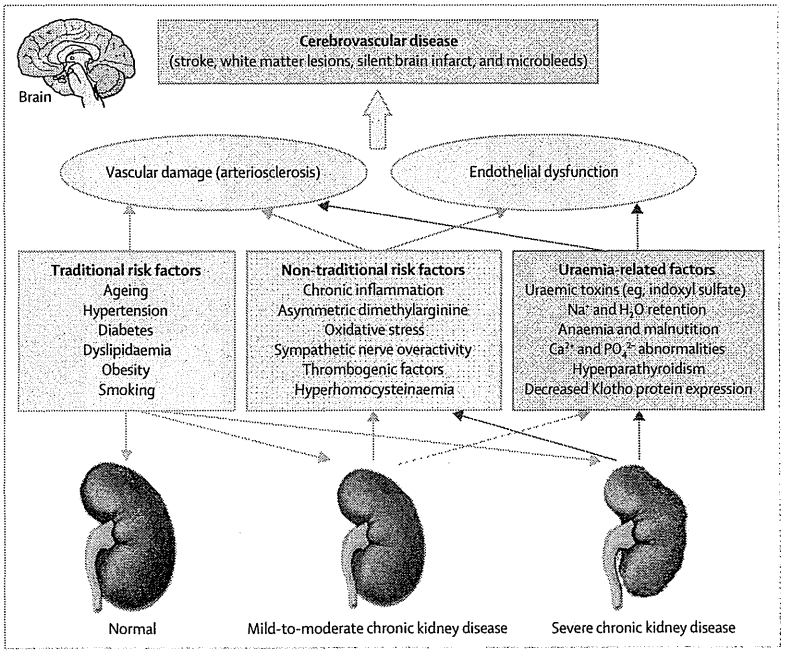

Figure 3: **Traditional and non-traditional risk factors for stroke and kidney disease**

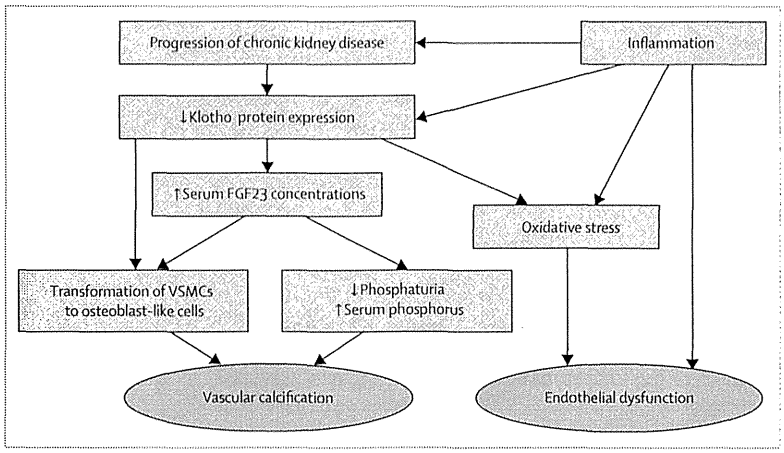

Figure 4: Effect of Klotho protein on vascular damage in patients with chronic kidney disease
FGF23=fibroblast growth factor 23. VSMC=vascular smooth muscle cell.

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]

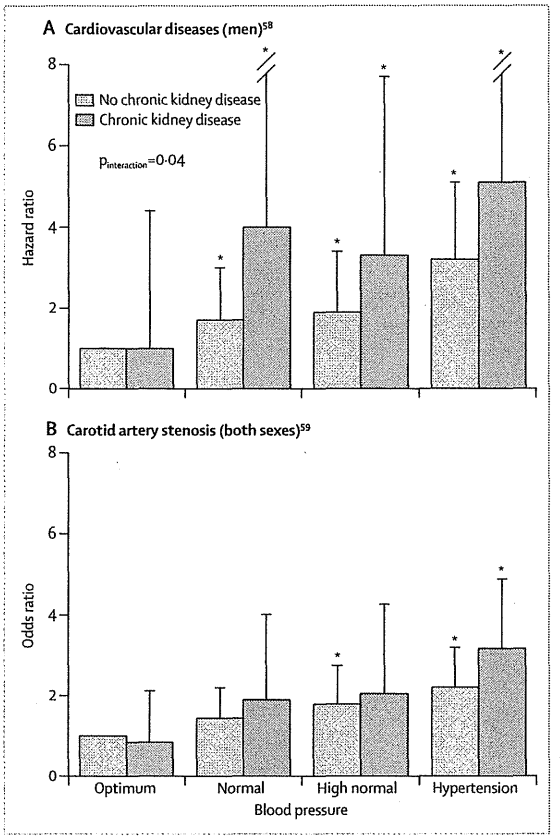

Figure 5: **The association between blood pressure and the effect of chronic kidney disease on clinical and subclinical cardiovascular diseases**
The combination of chronic kidney disease and blood pressure categories on (A) multivariate-adjusted hazard ratios for cardiovascular disease (men) and (B)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

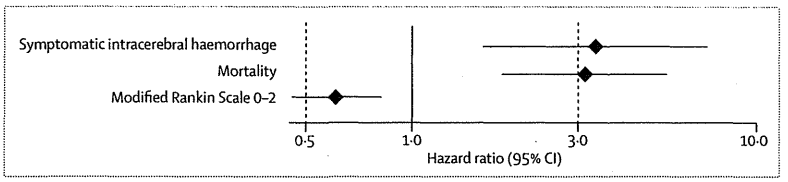

Figure 6: **Meta-analysis of symptomatic intracerebral haemorrhage, mortality, and outcome after intravenous thrombolysis in patients with chronic kidney disease**
Modified with permission from Hirano.[100] © S Kargar AG, Basel.

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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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]

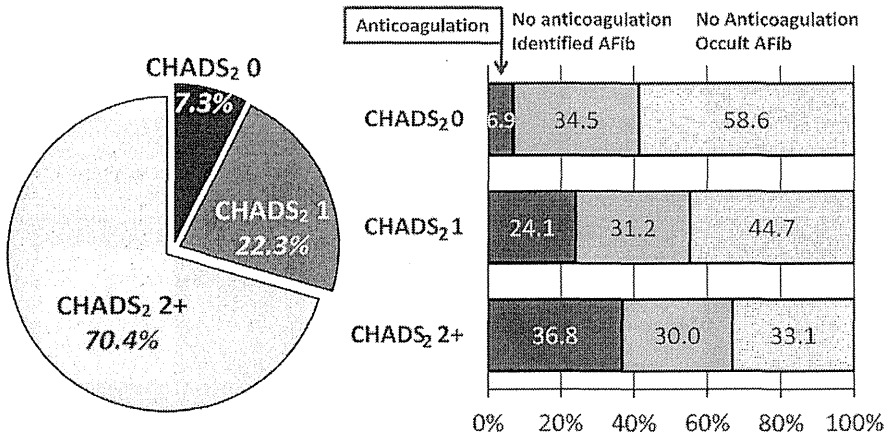

Figure 1. (Left) Percentages of patients with low (0), intermediate (1), and high (≥2) $CHADS_2$ scores prior to onset of index stroke or transient ischemic attack (TIA) who did or did not receive prestroke anticoagulation: the Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (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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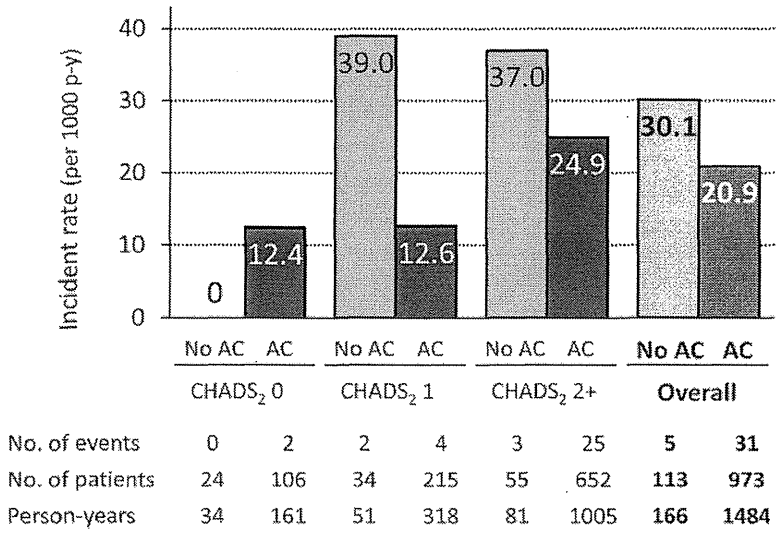

Figure 2. Rate of ischemic stroke in patients with and without anticoagulation (AC) according to ischemia risk by the CHADS2 score: the Bleeding with Antithrombotic Therapy (BAT) Study.

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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Trends in oral anticoagulant choice for acute stroke patients with nonvalvular atrial fibrillation in Japan: The SAMURAI-NVAF Study

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Background **Large clinical trials are lack of data on nonvitamin K antagonist oral anticoagulants for acute stroke patients.**

Aim **To evaluate the choice of oral anticoagulants at acute hospital discharge in stroke patients with nonvalvular atrial fibrillation and clarify the underlying characteristics potentially affecting that choice using the multicenter Stroke Acute Management with Urgent Risk-factor Assessment and Improvement-NVAF registry (ClinicalTrials.gov NCT01581502).**

Method **The study included 1192 acute ischemic stroke/transient ischemic attack patients with nonvalvular atrial fibrillation (527 women, 77·7 ± 9·9 years old) between September 2011 and March 2014, during which three nonvitamin K antagonist oral anticoagulant oral anticoagulants were approved for clinical use. Oral anticoagulant choice at hospital discharge (median 23-day stay) was assessed.**

Results **Warfarin was chosen for 650 patients, dabigatran for 203, rivaroxaban for 238, and apixaban for 25. Over the three 10-month observation periods, patients taking warfarin gradually decreased to 46·5% and those taking nonvitamin K antagonist oral anticoagulants increased to 48·0%. As compared with warfarin users, patients taking nonvitamin K antagonist oral anticoagulants included more men, were younger, more frequently had small infarcts, and had lower scores for poststroke $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED, admission National Institutes of Health stroke scale, and discharge modified Rankin Scale. Nonvitamin K antagonist oral anticoagulants were started at a median of four-days after stroke onset without early intracranial hemorrhage. Patients starting nonvitamin K antagonist oral anticoagulants earlier had smaller infarcts and lower scores for the admission National Institutes of Health stroke scale and the discharge modified Rankin Scale than those starting later. Choice of nonvitamin K antagonist oral anticoagulants was independently associated with 20-day or shorter hospitalization (OR 2·46, 95% CI 1·87–3·24).**

Conclusions **Warfarin use at acute hospital discharge was still common in the initial years after approval of nonvitamin K antagonist oral anticoagulants, although nonvitamin K antagonist oral anticoagulant users increased gradually. The index stroke was milder and ischemia-risk indices were lower in nonvitamin K antagonist oral anticoagulant users than in warfarin users. Early initiation of nonvitamin K antagonist oral anticoagulants seemed safe.**

Key words: acute stroke care, anticoagulation, atrial fibrillation, embolism, prevention

Introduction

Between 2009 and 2013, four novel oral anticoagulants, or in other words nonvitamin K antagonist (VKA) oral anticoagulants (NOACs) (1), were shown to be at least as effective for reducing stroke and as safe as warfarin, in particular more protective against intracranial hemorrhage (ICH) than warfarin, for patients with nonvalvular atrial fibrillation (NVAF) (2–5). These NOACs have a wider therapeutic range and fewer drug and food interactions than VKAs, and were also proven to be useful for secondary stroke prevention in patients with NVAF (6–8). The effect of NOACs seems to be clearer in Asians than in non-Asians (9,10). Of the NOACs, dabigatran (March 2011), rivaroxaban (April 2012), and apixaban (February 2013) began to be used clinically after official approval in Japan. The sudden increase in the options for oral anticoagulants (OACs) after long years of restricted choice of VKAs alone has brought confusion in the choice of the optimal OAC for each NVAF patient. In addition, the clinical trials on NOACs excluded acute stroke patients within 14 days after onset (within seven-days in ARISTOTLE) from enrollment (2–5). Thus, the optimal timing for beginning NOACs for acute stroke or transient ischemic attack (TIA) patients has not been clear.

The Stroke Acute Management with Urgent Risk-factor Assessment and Improvement (SAMURAI)-NVAF Study was a prospective, multicenter, observational study designed to determine choice of anticoagulant therapy during the acute and chronic stages of ischemic stroke/TIA and short- and long-term outcomes, including stroke recurrence and bleeding complications, in patients having NVAF. Eighteen Japanese stroke centers participated in the study (Supporting Information Appendix S1). The study was registered with ClinicalTrials.gov (NCT01581502) and the Japanese University Hospital Medical Information Network (UMIN) Clinical Trials Registry (UMIN000006930). In this initial report, the aim was to clarify the associations of underlying clinical characteristics and stroke/TIA features of the registered patients with choice of OACs at their hospital discharge. Another aim was to determine the timing of OAC initiation and the duration of acute hospital stay in patients on different OAC medications.

Methods

In the SAMURAI-NVAF Study, patients who were hospitalized (or initiated acute management at the outpatient clinic) within seven-days after onset of ischemic stroke/TIA and were diagnosed as having NVAF between September 2011 and March 2014 were enrolled. NVAF was diagnosed on 12-lead electrocardiogram or 24-h or longer monitoring for atrial fibrillation (AF) detection during acute hospitalization or from previous medical documents. Patients who met the following criteria were excluded: rheumatic mitral valve disease; a history of prosthetic valve replacement or mitral valve surgical repair; active infectious endocarditis; or lack of written informed consent by patients or next of kin. All study procedures were reviewed and approved by the local Ethics Committees.

Each patient was identified by a linkable patient identification code and was registered along with clinical information via the web-based registration system. Of the documented information, the variables listed in Table 1 were assessed in this study. The $CHADS_2$ and CHA_2DS_2-VASc scores as ischemic stroke risk indices and the HAS-BLED score as a bleeding-risk index were assessed both before and after onset of the index stroke/TIA (11–13).

As stroke features, infarct size was defined as small when the longest diameter was ≤15 mm; as large when the infarct was larger than one-third of the territory of the middle cerebral artery, anterior cerebral artery, posterior cerebral territory, or cerebellar hemisphere; and as medium for the others. Neurologic deficits were assessed using the National Institutes of Health stroke scale (NIHSS) score on admission and at seven-days after onset. Functional outcome was assessed using the modified Rankin Scale (mRS) score at acute hospital discharge (or 30 days after onset, whichever occurred first; median 23 days).

Patient eligibility for anticoagulant therapy and choice of OACs were determined by each investigator. In this study, OACs chosen on the day of acute hospital discharge (or 30 days after onset, whichever occurred first) were investigated. The clinical characteristics of patients taking different OACs at discharge were compared. Trends in the choice were compared according to three 10-month observation periods (September 2011 to June 2012, July 2012 to April 2013, and May 2013 to March 2014). In addition, the days until initiating OAC medication after stroke onset and the duration of acute hospital stay with the different OACs were evaluated.

Statistics

Data are presented as means ± SD, median values (interquartile range), or numbers (%). Underlying characteristics and stroke features were compared using χ^2 tests, unpaired *t*-tests, and Wilcoxon's test, as appropriate. Trends among the three periods were compared using χ^2 tests and one-way factorial analysis of variance, as appropriate. Days until starting OACs and those of hospital stay were compared using Kruskal–Wallis test. Multivariate logistic regression analysis was performed to identify parameters associated with short hospital stay using the forced entry method for potential confounding factors. All statistical analyses were conducted using JMP 9·0·2 statistical software (SAS Institute, Cary, NC, USA). A P value of <0·05 was considered significant.

Results

A total of 1192 patients (527 women, 77·7 ± 9·9 years old) were registered in the study. All patients were hospitalized. Of these, 820 patients (68·8%) were admitted on the day of onset, 234 (19·6%) on the next day, and 138 (11·6%) two-days or later after onset. The underlying characteristics and stroke features of the patients are listed in Table 1. The median admission NIHSS score was 8 [interquartile range (IQR) 2–18], and the median discharge mRS score was 3 (1–4). Supporting Information Fig. S1 shows changes in $CHADS_2$, CHA_2DS_2-VASc, and HAS-BLED scores before and after developing the index stroke/TIA. The median