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Original Article

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Renal dysfunction in acute stroke: an independent predictor of long-term all combined vascular events and overall mortality

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Abstract

Background. Acute stroke is the third leading cause of death in western societies after ischemic heart disease and cancer. Although it is an emergency disease sharing the same atherosclerotic risk factors with ischemic heart disease, the association of renal function and stroke is poorly investigated. The present study aims at assessing renal function status in patients with acute stroke and investigate any prognostic significance on the outcome.

Methods. This is a prospective study of hospitalized first-ever stroke patients over 10 years. The study population comprised 1350 patients admitted within 24 h from stroke onset and followed up for 1 to 120 months or until death. Patients were divided in 3 groups on the basis of the estimated Glomerular Filtration Rate (eGFR) that was calculated from the abbreviated equation of the Modification Diet for Renal Disease in ml/min/1.73m^2 of body surface area: Group-A comprised patients who had eGFR > 60, group-B those with $30 \leq$ eGFR ≤ 60 and group-C patients with eGFR < 30. Patients with Acute Kidney Injury (AKI) were excluded from the study. The main outcome measures were overall mortality and the composite new cardiovascular events (myocardial infarction, recurrent stroke, vascular death) among the 3 groups during the follow-up period.

Results. Almost 1/3 (28.08%) of our acute stroke patients presented with moderate (group B) or severe (group C) renal dysfunction as estimated by eGFR. After adjusting for basic demographic, stroke risk factors and stroke severity on admission, eGFR was an independent predictor of stroke mortality at 10 years. Patients in groups B and C had an increased probability of death during follow-up: Hazard ratio $= 1.21$ with 95% CI 1.01–1.46, $p < 0.05$ and Hazard ratio $= 1.76$ with 95% CI 1.14–2.73, $p < 0.05$ respectively, compared to patients belonging to group A. The probability of death from any cause was significantly different among groups (log rank test 55.4, $p = 0.001$) during the follow-up period: in group-A patients it was 62.8 (95% CI 57.6–68.1), in group-B 77.3 (95% CI 68.5–86.1) and in group-C 89.2 (95% CI 75.1–100). During the follow-up period 336 new cardiovascular events occurred. The probability to have a new composite cardiovascular event was also significantly different among the 3 groups (log rank test 21.1, $p = 0.001$): in group-A patients it was 45.2 (95% CI 38.7–51.7), in group-B 67.4 (95% CI 56.2–78.6) and in group-C 77.6 (95% CI 53.5–100).

Conclusion. Renal function on admission appears to be a significant independent prognostic factor for long term mortality and new cardiovascular morbidity over a 10-year period.

Keywords: acute stroke; cardiovascular morbidity; chronic kidney disease; renal dysfunction; mortality

Introduction

Stroke represents a continuously evolving medical and social problem, being the third leading cause of death after heart disease and cancer in developed countries [1]. The increasing economic burden that patients with stroke impose on the already 'overloaded' social security systems of western societies, as well as the significant loss of manpower, renders the study of prognostic factors that can affect short- and long-term mortality after stroke indispensable. In previous years, several factors, such as C-reactive protein, glucose levels on admission, fibrinogen concentration, erythrocyte sedimentation rate, leukocyte count, uric acid and a low tri-iodothyronine level, have been associated with a low survival rate after acute stroke [2–5].

Renal function impairment has been associated with a high prevalence of cardiovascular disease (CVD) [6]. Patients with reduced renal function are at high risk for the subsequent development of CVD disease including stroke [7–9]. Several studies in the last decade revealed that not only the risk of mortality but also the new cardiovascular events after myocardial infarction or heart failure are higher

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among patients with renal dysfunction [10–13]. Although acute stroke is an emergency disease and shares the same atherosclerotic risk factors with ischaemic heart disease, the association of renal function and stroke is poorly investigated. Friedman investigated elderly stroke survivors and found that serum creatinine concentration independently predicted mortality during a follow-up period of 18 months [14]. More recently, Mc Walter *et al.* showed in a larger group of acute stroke patients that mortality was higher among patients with reduced renal function on admission [15]. However, stroke is a vascular disease, and it is important for the development of both preventive and therapeutic strategies to identify the role of renal function on global cardiovascular risk after an acute stroke [16].

The aim of the present study was to investigate the role of renal function in patients admitted for acute first-ever stroke on (a) overall mortality and (b) on subsequent composite vascular events over a 10-year period.

Subjects and methods

Study population

From a consecutive series of first-ever acute stroke patients, 1350 were admitted to our acute stroke unit or medical wards within 24 h after symptoms onset between January 1995 and December 2005. All patients were included in 'The Athens Stroke Registry', a prospective observational stroke data bank. Details of this study and exclusion criteria have been previously described [17]. All patients were examined on admission by an internist specialized in stroke or a neurologist, and stroke severity was assessed using the Scandinavian Stroke Scale (SSS) [18]. The total score of the scale ranges from 2 (minimum) to 58 (maximum). The score decreases with the severity of stroke.

Data sources and study outcomes

Upon admission, a standard blood sample was obtained for complete blood count, coagulation tests, serum electrolytes, glucose and renal function tests (urea, creatinine levels). An initial brain computerized tomography (CT) scan and a 12-lead electrocardiogram were immediately performed while Doppler ultrasonography of the cervical arteries was performed during the first 24 h of hospitalization. A second CT or magnetic resonance imaging scan was later performed, and films were evaluated by two independent neuroradiologists. Renal function tests were performed daily during hospitalization. Stroke risk factors were recorded based on previously defined criteria [17]. A history of hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg, or both, diagnosed at least twice before the stroke or treatment of hypertension had been implemented. Current smoking was considered present when a subject had smoked daily prior to the stroke. The presence of diabetes mellitus was defined as the use of a blood-sugar-lowering drug before the occurrence of the stroke or if the fasting blood glucose level exceeded >6.0 mmol/l known before the stroke. Hypercholesterolaemia was defined by history or if a cholesterol concentration of >6.5 mmol/l was detected the day after admission. A history of a transient ischaemic attack (TIA) was defined when a subject had a TIA diagnosed by a neurologist as a temporary, focal neurological deficit presumably related to ischaemia and lasting <24 h. A history of coronary heart disease (myocardial infarction, angina pectoris) was assessed by questionnaire and relevant medical confirmation. Stroke was defined according to World Health Organization criteria [19]. Pathological stroke subtype (ischaemic versus haemorrhagic) was established by brain imaging. Cerebral oedema was defined as the presence of midline shift, sulcal effacement or ventricular compression in acute ischaemic stroke patients [20] and as a hypodense area around the hyperdense haematoma accompanied by the mass effect in patients with intracerebral haemorrhage [21].

Renal function on admission was assessed using the abbreviated equation of the Modification Diet for Renal disease (MDRD) that estimates the glomerular filtration rate (eGFR) from the following formula [22]:

$$\begin{aligned}\text{eGFR (in ml/min per 1 .73 m}^2) &= 186.3 \\ &\times \text{Serum Creatinine (exp}[-1.154]) \times \text{Age (exp}[0.203]) \\ &\times (0.742 \text{ if female}) \times (1.21 \text{ if black}).\end{aligned}$$

Since the use of the MDRD formula requires that renal function is in a steady state, patients with acute kidney injury (AKI) were identified and excluded from the study. The absolute or relative change in serum creatinine was used to define AKI [absolute increase in serum creatinine of either ≥0.3 mg/dl (≥25 μmol/l) or a percentage increase of ≥50%, on the basis of the ADQI definition] [23].

Patients were divided into three groups on the basis of eGFR: group A comprised patients with eGFR >60 ml/min/1.73 m^2 of body surface area (BSA), group B those with 60 ≥ eGFR ≥ 30 ml/min/1.73 m^2 of BSA and group C patients with eGFR <30 ml/min/1.73 m^2 of BSA.

All patients were followed up prospectively at months 1, 3 and 6, and every 6 months thereafter, up to 10 years after stroke by a study investigator and a trained nurse. Follow-up was routinely performed in our outpatient clinic or in the patient's place of residence in cases with severe handicap. The outcome events of interest were death from any cause and the composite all cardiovascular events (fatal and non-fatal). To determine recurrent vascular events and causes of death, we evaluated all the available information obtained from death certificates, hospital records, physicians' notes in private practice, necropsy findings and the patients' clinical presentation at the regular follow-up assessments. The composite cardiovascular events included recurrent stroke, new myocardial infarction or unstable angina, new onset of heart failure, sudden death with or without resuscitation, clinical onset of peripheral arteriopathy and thoracic or abdominal aortic rupture [24]. Recurrent stroke was defined as a cerebrovascular event of sudden onset lasting for >24 h subsequent to the initial stroke that clearly resulted in a new (or an increase in an existing) neurological deficit [25].

Statistical analysis

Statistical analysis was performed to compare patients belonging to the three groups (A, B and C). Categorical variables were compared with the chi-square test, and continuous variables were compared using the one-way ANOVA test. Continuous data are presented as mean (SD) and categorical data as percentages. The Kaplan–Meier product limit method and the log-rank test were used to estimate the probability of survival and the probability of the composite cardiovascular events at 10 years after the index event. During the follow-up, 80 patients were lost to follow-up and their survival data were censored at the last time they were known to be alive. To evaluate which factors contribute to 10-year mortality, a univariate Cox's proportional hazards model was used. Those factors that were found to contribute to the outcome in the univariate analyses at *P*-values <0.1 were included in the multivariate model. In the multivariate analyses, statistical significance was reached if $P < 0.05$. Associations are presented as hazard ratios (HR) with their corresponding 95% confidence intervals (95% CI). The Statistical Package for Social Science (SPSS Inc., version 15.0 for Windows) was used.

Results

The patient population selected for the present study ($n = 1193$) consisted of 729 male and 464 female subjects (mean age 71.1 ± 11.3) after the exclusion of 193 (14.29%) patients that developed AKI. Study patients were followed up for 1–120 months or until death [mean time of observation was 36.5 months (SD 35.4)]. The mean time delay to hospital admission was 5.7 ± 6.8 h and was not correlated toGFR ($r = -0.04$, $P = 0.23$). Based on the formula of the renal function estimation, 858 (71.9%) stroke patients had an eGFR >60 ml/min/1.73 m^2, 305 (25.6%) patients had 30 ≤ eGFR ≤ 60 ml/min/1.73 m^2 and 30 (2.5%) patients with eGFR <30 ml/min/1.73 m^2. The eGFR at baseline for the 1193 patients with a serum creatinine measurement was normally distributed (Figure 1). Basic characteristics of the patients are presented in Table 1. Patients with an eGFR <30 ml/min/1.73 m^2 presented with the most severe stroke compared to the other two groups as measured by the SSS estimation. Differences among the three groups were also seen in age, sex, history of hypertension, smoking, atrial fibrillation and glucose levels on admission.

In the multivariate analysis, several factors correlated to 10-year mortality (Table 2). Cox proportional hazard analysis showed that increasing age, ischaemic heart disease, atrial fibrillation, decreasing SSS score, high glucose on

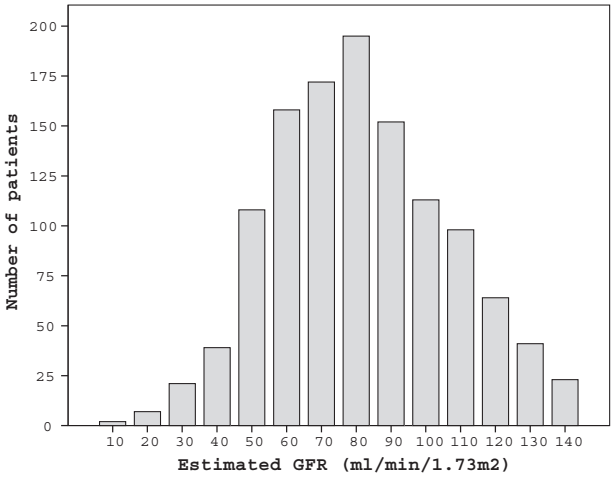

Fig. 1. Distribution of estimated GFR on admission for the 1350 patients with a serum creatinine measurement.

Table 1. Demographics, risk factors and clinical and laboratory characteristics of 1193 acute stroke patients according to estimated GFR (ml/min/1.73 m^2)

	GFR > 60	30 ≤ GFR ≤ 60	GFR < 30	
Characteristic	(*N* = 858)	(*N* = 305)	(*N* = 30)	*P*-value
Mean age (years, SD)	69.7 (11.5)	74.7 (10.0)	76.6 (8.8)	0.000
Sex (male)	561 (65.4)	159 (52.1)	9 (30.0)	0.000
History of				
Hypertension	567 (66.1)	232 (76.1)	28 (93.3)	0.000
Diabetes mellitus	203 (23.7)	88 (28.9)	7 (23.3)	NS
Hypercholesterolaemia	271 (31.6)	81 (26.6)	7 (23.3)	NS
Cigarette smoking	288 (33.6)	73 (23.9)	8 (26.7)	0.007
Previous transient ischaemic attacks	97 (11.3)	29 (9.5)	2 (6.7)	NS
Coronary artery disease	174 (20.3)	71 (23.3)	9 (30.0)	NS
Atrial fibrillation	270 (31.5)	121 (39.7)	14 (46.7)	0.011
Clinical presentation				
Neurological impairment[a]	33.3 (19.4)	30.5 (19.6)	25.1 (20.2)	0.011
Ischaemic infarction	725 (84.5)	259 (84.9)	27 (90.0)	NS
Intracerebral Haemorrhage	133 (15.5)	46 (15.1)	3 (10.0)	NS
Laboratory findings				
Brain oedema on CT	201 (23.4)	77 (25.2)	10 (33.3)	NS
Glucose on admission (100 mg/dl)	129.7 (56.3)	143.8 (66.6)	136.4 (52.8)	0.003
Creatinine on admission (mg/dl)	0.86 (0.19)	1.35 (0.23)	3.02 (2.04)	0.000

GFR, glomerular filtration rate.
Numbers in parentheses for nominal data indicate percentages and for continuous SD.
[a]Neurological impairment on admission assessed by the Scandinavian Stroke Scale (2–58, 2 = worst score, 58 = best score).

Table 2. Multivariate Cox proportional hazard analyses determining the effect of different factors on 10-year mortality and on the occurrence of composite cardiovascular events over 10 years

Dependent variable	10-year overall mortality Hazard ratio (95% CI)	10-year composite cardiovascular events Hazard ratio (95% CI)
Age (per 10-year increase)	1.84 (1.66–2.03)*	1.37 (1.22–1.54)†
Previous transient ischaemic attacks		1.57 (1.15–2.14)#
Coronary artery disease	1.43 (1.18–1.73)*	1.43 (1.12–1.82)#
Atrial fibrillation	1.22 (1.02–1.46)#	1.30 (1.03–1.63)†
Stroke severity (per 10-point increase in SSS score)	0.75 (0.71–0.78)*	
Glucose on admission (per 10 mg/dl increase)	1.03 (1.02–1.05)*	1.02 (1.01–1.04)#
Renal function		
GFR $\geq$ 60 (reference point)	1.00	1.00
30 $\leq$ GFR $<$ 60	1.21 (1.01–1.46)†	1.29 (1.01–1.64)†
GFR $<$ 30	1.76 (1.14–2.73)†	1.86 (1.05–3.29)†

GFR, glomerular filtration rate; CI, confidence interval; SSS score, Scandinavian Stroke Scale score (2–58 points).
*$P < 0.001$, #$P < 0.01$, †$P < 0.05$.

admission and lower eGFR remained as independent predictors of 10-year mortality. Patients belonging to groups B and C had an increased probability of death over 10 years: hazard ratio = 1.21 with 95% CI 1.01–1.46, $P < 0.05$ and hazard ratio = 1.76 with 95% CI 1.14–2.73, $P < 0.05$, respectively, compared to patients belonging to group A (Table 2). In the Kaplan–Meier analysis, the 10-year mortality rate was 62.8 (95% CI 57.6–68.1) for group A patients, 77.3 (95% CI 68.5–86.1) for group B and 89.2 (95% CI 73.3–100.0) for group C patients (Figure 2, Table 3).

During the follow-up period, 336 cardiovascular events occurred: 188 recurrent strokes, 50 myocardial infarctions, 41 new cases of heart failure leading to death, 48 sudden deaths of presumed vascular origin, 4 aortic aneurysm rupture and 5 new cases of symptomatic peripheral atherosclerotic arterial disease. After adjusting for the baseline factors in the multivariate Cox regression model, renal function as measured by the estimated GFR, along with age, history of TIAs, coronary artery disease, atrial fibrillation and glucose on admission, was an independent predictor of the overall composite cardiovascular events during the follow-up (Table 2). Using group A as the reference group, the adjusted hazard ratio for the composite cardiovascular events was 1.29 (95% CI, 1.01–1.64, $P < 0.05$) for patients belonging to group B and 1.86 (95% CI, 1.05–3.29, $P < 0.05$) for those in group C (Table 2). In the Kaplan–Meier analysis, an early divergence of the curves of the composite cardiovascular events was observed across the three groups of eGFR (Figure 3). The probability of having a composite cardiovascular event over the follow-up period was (log-rank test 21.1, $P = 0.001$) as follows: in group A patients 45.2 (95% CI 38.7–51.7), in group B 67.4 (95% CI 56.2–78.6) and in group C 77.6 (95% CI 53.5–100) (Figure 2, Table 3).

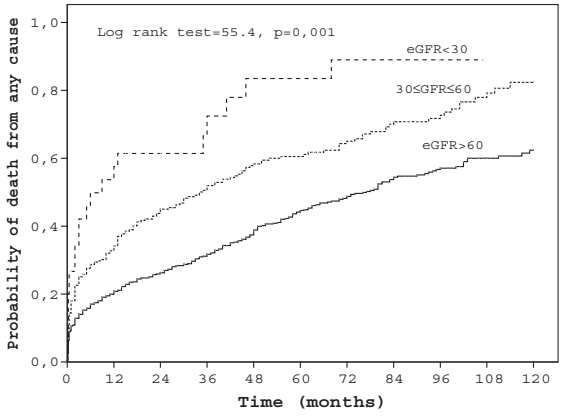

Fig. 2. Kaplan–Meier estimates of probability of death from any cause in patients with acute stroke over a period of 10 years according to estimated GFR (ml/min/1.73 m^2) on admission.

Discussion

Our study showed that renal function on admission is a strong independent prognostic factor for long-term mortality and new cardiovascular morbidity following stroke over a 10-year period. Almost one-third (28.08%) of our acute stroke patients presented with moderate (group B) or severe (group C) renal dysfunction as estimated by eGFR suggesting a significant prevalence of chronic kidney disease (CKD) in this cohort. We found that the presence of even moderate renal dysfunction during the acute phase independently predicted new cardiovascular events for a long period of time.

By using the eGFR, we identified a significant prevalence of renal dysfunction, in patients presenting early to the hospital with acute stroke (<24 h). In the Mc Walter *et al.* [15] study, a similar high proportion of patients who presented within 48 h of ictus had renal dysfunction despite the differences in the risk profile of patients. In our cohort, the high frequency of renal dysfunction might be explained in part by the higher coexistence of hypertension that was increased in the lower eGFR values. In order to assess the true prevalence of CKD and its role on long-term mortality and occurrence of cardiovascular events, we identified patients with AKI and excluded them from the study. AKI is an independent prognostic factor for mortality after

Table 3. Cumulative overall mortality and cumulative probability of composite cardiovascular events in patients with acute stroke according to estimated GFR (ml/min/1.73 m^2)

	GFR > 60	30 ≤ GFR ≤ 60	GFR < 30	*P*-value
Cumulative mortality (95% CI)				
1 month	10.5 (8.3–12.7)	17.6 (13.1–22.1)	21.4 (6.1–36.7)	0.003
1 year	20.6 (17.7–23.5)	33.6 (27.7–39.5)	54.5 (34.9–74.1)	0.001
10 years	62.8 (57.6–68.1)	77.3 (68.5–86.1)	89.2 (75.1–100)	0.001
Cumulative probability of composite cardiovascular events (95% CI)				
1 month	3.8 (2.4–5.2)	6.6 (3.5–9.7)	9.1 (2.9–21.1)	0.098
1 year	13.3 (10.6–15.8)	17.8 (12.7–22.9)	36.0 (12.7–59.3)	0.021
10 years	45.2 (38.7–51.7)	67.4 (56.2–78.6)	77.6 (53.5–100)	0.001

GFR, glomerular filtration rate; CI, confidence interval.
P-values by the log-rank test.

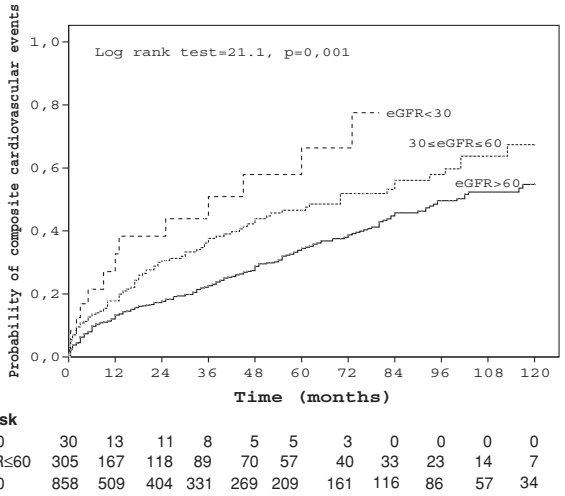

Fig. 3. Kaplan–Meier estimates of probability of composite cardiovascular events in patients with acute stroke over a period of 10 years according to estimated GFR (ml/min/1.73 m^2) on admission.

stroke and was present in 14.29% of our patients (a finding consistent with a recent study) [26].

We have shown that even a moderate reduction in renal function appeared to be an independent and clinically relevant risk factor not only for the overall mortality but also for the composite fatal and nonfatal cardiovascular events. The role of renal dysfunction was apparent early (1 month) after the acute event and persisted continuously for a long period (10 years). A few previous studies reported mortality data, with limited information on nonfatal cardiovascular events. Friedmann conducted a small (492 patients) study in New Zealand and found that serum creatinine independently predicted mortality in stroke survivors followed for a period of 18 months [14]. Mc Walter *et al.* studied a large number of unselected consecutive acute stroke patients; according to their results, patients with renal dysfunction as estimated by creatinine clearance, urea concentrations and the ratio of urea to creatinine had a higher mortality risk during the 7-year follow-up period [15]. However, patients with AKI were not identified and excluded from the study and the effect of renal function on fatal and nonfatal cardiovascular events was not investigated. Our findings further highlight the importance of estimating the degree of renal dysfunction in patients presenting with acute stroke since it predicts early nonfatal events and also has a significant predictive value for a long time period.

It is interesting that many studies examining patients with acute myocardial infarction have also shown a close relationship between baseline renal impairment and increased mortality [10–12,27,28] and/or morbidity [12]; these results and those obtained in the current study examining acute stroke patients are similar. Furthermore, in the valsartan in Acute Myocardial Infarction Trial, Anavekar *et al.* found that each reduction of the estimated GFR by 10 units at baseline was associated with a hazard ratio for death and nonfatal cardiovascular events of 1.10 (95% CI, 1.08–1.12) [12].

The interaction of kidney function and CVD has been the subject of many recent analyses. There is ongoing evidence that CKD is an additional risk factor for CVD including stroke [29–31]. This association is mainly explained by shared biological mechanisms predisposing to the development of clinical atherosclerosis in the renal, coronary and cerebral vasculature. Traditional cardiovascular risk factors, in particular hypertension and diabetes, could lead to a similar vascular injury in both kidney and brain and explain these associations. Autopsy data have shown that atherosclerotic renal artery stenosis is common in patients with stroke, especially in those with brain infarction [32]. In addition, recent studies showed a close relationship between renal dysfunction and stroke due to small vessel diseases. The brain and kidney share a similar vascular structure with low-resistance exposure of the small vessels to highly pulsatile flow and pressure [33]. As a result, microvascular damage to both organs can lead not only to renal impairment with reduced GFR but also to asymptomatic or symptomatic brain infarcts and white matter lesions [34–36]. We cannot provide data concerning the presence of coexisting asymptomatic lesions on brain-imaging studies for our symptomatic patients in relation to renal function. Further studies using MRI techniques are needed to provide more data on this topic.

Our results suggest that estimated GFR may be a useful tool to identify patients at high risk of death and nonfatal cardiovascular events in patients presenting with acute stroke. Using simple measurements of serum creatinine

levels, we might have missed many patients at risk. Recent recommendations in hypertension management introduce the use of equations for GFR estimation or the measurement of creatinine clearance as routine laboratory tests [37]. There are no studies examining the effect of renal function improvement on stroke outcome. Our findings support the need of future research to clarify the mechanisms of adverse cardiovascular outcomes associated with impaired renal function; addressing the possibility of therapeutic interventions to try and improve renal function in these patients may be crucial.

Our study has several limitations. First, the study is hospital based and not population based, and stroke patients treated at home are not included. Secondly, although the use of the MDRD equation is a quite reliable means of estimating GFR and has been previously used in many clinical trials, it tends to overestimate GFR in high levels of renal function and is inversely affected by age. Despite these limitations, our study reinforces the belief that renal function is an important and significant independent prognostic factor for mortality and cardiovascular events after acute stroke.

Conclusions

In this observational study of patients with acute stroke, reduced estimated GFR appears to be a significant independent risk factor for short- as well as long-term mortality and new cardiovascular morbidity. This finding suggests that estimated GFR should be added to the other known prognostic factors and emphasizes the importance of identification and management of unrecognized chronic kidney disease in stroke therapy.

Conflict of interest statement. None declared.

References

1. Mackay J, Mensah G. *The Atlas of Heart Disease and Stroke*. World Health Organization (WHO) in collaboration with the Centers for Disease Control and Prevention, 2004. Available at: http://www.who.int/cardiovascular_diseases/resources/atlas/en/
2. Capes SE, Hunt D, Malmberg K *et al*. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke* 2001; 32: 2426–2432
3. Kannel WB, Anderson K, Wilson PWF. White cell blood count and cardiovascular disease: insights from the Framingham study. *JAMA* 1992/2004; 267: 1253–1256
4. Rundek T, Sacco RL. Outcome following stroke (chapter 3). In: Mohr JP, Choi DW, Grotta JC, Weir B, Wolf PA (eds). *Stroke Pathophysiology, Diagnosis, and Management*, 5th edn. New York: Churchill Livingstone, 2004, 35–57
5. Alevizaki M, Synetou M, Xynos K *et al*. Low triiodothyronine: a strong predictor of outcome in acute stroke patients. *Eur J Clin Invest* 2007; 37: 651–665
6. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol* 1998; 9(Suppl): S16–S23
7. Sarnak MJ, Levey AS, Schoolwerth AC *et al*. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 2003; 42: 1050–1065
8. Weiner DE, Tighiouart H, Amin MG *et al*. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol* 2004; 15: 1307–1315
9. Foley RN, Murray AM, Li S *et al*. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol* 2005; 16: 489–495
10. Wright RS, Reeder GS, Herzog CA *et al*. Acute myocardial infarction and renal dysfunction: a high-risk combination. *Ann Intern Med* 2002; 137: 563–570
11. Al Suwaidi J, Reddan DN, Williams K *et al*. Prognostic implications of abnormalities in renal function in patients with acute coronary syndromes. *Circulation* 2002; 106: 974–980
12. Anavekar NS, McMurray JJV, Velazquez E *et al*. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. *N Engl J Med* 2004; 351: 1285–1289
13. Smith GL, Lichtman JH, Bracken MB *et al*. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. *J Am Coll Cardiol* 2006; 47: 1987–1996
14. Friedman PJ. Serum creatinine: an independent predictor of survival after stroke. *J Inter Med* 1991; 229: 175–179
15. Mc Walter RS, Wong SYS, Wong KYK *et al*. Does renal dysfunction predict mortality after acute stroke? A 7-year follow-up study. *Stroke* 2002; 33: 1630–1635
16. Sacco RL. The 2006 William Feinberg Lecture: shifting the paradigm from stroke to global vascular risk estimation. *Stroke* 2007; 38: 1980–1987
17. Vemmos KN, Takis CE, Georgilis K *et al*. The Athens stroke registry: results of a five-year hospital-based study. *Cerebrovasc Dis* 2000; 10: 133–141
18. Lindestrom E, Boysen G, Christiansen LW *et al*. Reliability of scandinavian neurological stroke scale. *Cerebrovasc Dis* 1991; 1: 103–111
19. Hatano S. Experience from a multicentre stroke register: a preliminary report. *Bull WHO* 1976; 54: 541–553
20. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke* 1997; 28: 2109–2118
21. Dul K, Drayer B. CT and MR imaging of intracerebral hemorrhage. In: Kase CS, Caplan LR (eds). *Intracerebral Hemorrhage*. Boston, MA: Butterworth-Heinemann, 1994, 73–93
22. Levey AS, Bosch JP, Lewis JB *et al*. Modification of Diet in Renal Disease Study Group. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999; 130: 461–470
23. Mehta RL, Kellum JA, Shah SV *et al*. Acute Kidney Injury Network (AKIN): report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; 11: R31
24. Pfeffer MA, McMurray JJ, Velazquez EJ *et al*. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003; 349: 1893–1906
25. EAFT (European Atrial Fibrillation Trial) Study Group Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet* 1993; 342: 1255–1262
26. Covic A, Schiller A, Mardare NG *et al*. The impact of acute kidney injury on short-term survival in an Eastern European population with stroke. *Nephrol Dial Transplant* 2008; 23: 2228–2234
27. Chertow GM, Normand SLT, Silva LR *et al*. Survival after acute myocardial infarction in patients with end-stage renal disease: results from the Cooperative Cardiovascular Project. *Am J Kidney Dis* 2000; 35: 1044–1051
28. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 1998; 339: 799–805
29. Sarnak MJ, Levey AS, Schoolwerth AC *et al*. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular

Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. *Hypertension* 2003; 42: 1050–1065
30. Schiffrin EF, Lipman ML, Mann JFE. Chronic kidney disease. Effects on the cardiovascular system. *Circulation* 2007; 116: 85–97
31. Wannamethee SG, Shaper AG, Perry IJ. Serum creatinine concentration and risk of cardiovascular disease: a possible marker for increased risk of stroke. *Stroke* 1997; 28: 557–563
32. Kuroda S, Nishida N, Uzu T *et al*. Prevalence of renal artery stenosis in autopsy patients with stroke. *Stroke* 2000; 31: 61–65
33. O'Rourke MF, Safar ME. Relationship between aortic stiffening and microvascular disease in brain and kidney: cause and logic of therapy. *Hypertension* 2005; 46: 200–204
34. Seliger SL, Longstreth WT Jr, Katz R *et al*. Cystatin C and subclinical brain infarction. *J Am Soc Nephrol* 2005; 16: 3721–3727
35. Khatri M, Wright CB, Nickolas TL *et al*. Chronic kidney disease is associated with white matter hyperintensity volume: the Northern Manhattan Study (NOMAS). *Stroke* 2007; 38: 3121–3126
36. Ikram MA, Vernooij MW, Hofman A *et al*. Kidney function is related to cerebral small vessel disease. *Stroke* 2008; 39: 55–61
37. Mancia G, De Backer G, Dominiczak A *et al*. ESH-ESC Task Force on the Management of Arterial Hypertension. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension. *J Hypertens* 2007; 25: 1751–1762

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