Archives of Clinical Nephrology

Peertechz

Fabio Fabbian[1]*, Cristiano Azzini[2], Mauro Gentile[3], Alfredo De Giorgi[1], Alessandro De Vito[2], Francesco Portaluppi[1] and Ilaria Casetta[3]

[1]*Clinica Medica, Azienda Ospedaliera-Universitaria of Ferrara, via Aldo Moro 8, I-44124 Cona, Ferrara, Italy*

[2]*Department of Neurosciences and Rehabilitation, Section of Neurology, University Hospital "S. Anna", Ferrara, Italy*

[3]*Department of Biomedical and Surgical Sciences, Section of Clinical Neurology, University of Ferrara, Italy*

Dates: Received: 07 May, 2015; **Accepted:** 27 May, 2015; **Published:** 01 June, 2015

***Corresponding author:** Fabio Fabbian, MD, Clinica Medica, Azienda Ospedaliera-Universitaria of Ferrara, via Aldo Moro 8, I-44124 Cona, Ferrara, Italy, Tel: +39-0532-237071; Fax: +39-0532-236816; E-mail: f.fabbian@ospfe.it

www.peertechz.com

Keywords: Chronic kidney disease; Glomerular Filtration Rate; Stroke; Intravenous Thrombolysis; Complications

Research Article

Impact of Glomerular Filtration Rate on Intravenous Thrombolytic Therapy in Acute Ischemic Stroke: A Retrospective Study from a Single Italian Center

Abstract

Aim: Chronic kidney disease (CKD) is a risk factor for stroke and in-hospital mortality due to stroke. Stroke is highly prevalent in CKD patients. Our aim was to evaluate the impact of glomerular filtration rate in acute ischemic stroke (IS) patients after thrombolytic therapy.

Methods: All patients who underwent thrombolytic therapy for acute IS in our Department between 2009 and 2012 were studied retrospectively. Age, co-morbidities, blood pressure, glycaemia, National Institutes of health Stroke Scale score were evaluated. Renal function was estimated by CKD-EPI equation. Three-month outcome (death, residual disability, intracranial hemorrhage) in patients with glomerular filtration rate (GFR) <60 ml/min/1.73m2 was compared to that of patients with GFR ≥ 60 ml/min/1.73 m2. Logistic regression analysis was used to determine which factor was independently associated with outcome.

Results: Among 191 patients treated for acute IS, 74 had GFR<60 ml/min/1.73m2. They were older and had higher prevalence of hypertension than patients with normal filtration rate. We found no differences in 3-month death or poor outcome between the two groups. However, patients with impaired renal function had a significantly higher risk of hemorrhagic complication (OR = 2.5; 95% CI = 1.1-6.2, p<0.01).

Conclusion: GFR<60 ml/min/1.73m2 significantly affects the risk of intracranial hemorrhage in stroke patients treated with thrombolytic therapy. Hence, subjects with reduced renal function eligible for intravenous thrombolysis could be informed about the increased ICH risk.

Abbreviations

CKD: Chronic Kidney Disease; IS: Ischemic Stroke; GFR: Glomerular Filtration Rate; rt-PA: recombinant tissue Plasminogen Activator; ICH: Intracranial Hemorrhage; NINDS: National Institute of Neurological Disorders and Stroke; ASPECTS: Alberta Stroke Program Early CT Score; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Score; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; SCr: Serum Creatinine; OR: Odds Ratios; CVAs: Cerebrovascular Accidents

Background

Intravenous recombinant tissue plasminogen activator (rt-PA) is a well-established treatment for acute ischaemic stroke (IS). In chronic kidney disease (CKD) the balance between bleeding and thrombosis is altered [1]. CKD is a well-established risk factor for in-hospital mortality due to myocardial infarction [2], and in this population, subjects receiving an early myocardial revascularization had the highest major bleeding rate [3]. CKD is also a risk factor for stroke [4] and in-hospital mortality due to stroke [5,6]. Moreover emergency department physicians could identify high risk subjects by simultaneous calculation of risk of stroke and GFR due to the fact that 10-year risk of stroke increases with worsening renal function [7]. The best treatment aiming to reduce mortality in population with CKD has not been established yet, and diagnostic and therapeutic interventions have been underutilized in the management of acute cardiovascular disease [8], and therapeutic nihilism has been described [9]. Physicians could be consulted for an opinion on rt-PA treatment when glomerular filtration rate (GFR) is low, since symptomatic intracranial haemorrhage (ICH) currently affects about 7% of such cases [10]. On the other hand renal function has not been reported to impact pharmacokinetics and metabolism of rt-PA [11]. The aim of this study was to evaluate retrospectively patients with acute IS treated with intravenous rt-PA as a part of the stroke treatment protocol; they were stratified on the basis of renal function evaluated on the basis of GFR measured on admission.

Methods

The study was approved by the Provincial Ethics Committee of Ferrara (Comitato Etico della Provincia di Ferrara), and it was carried out under the terms of the Declaration of Helsinki as revised in 2000.

We retrospectively analyzed the database of IS patients, admitted to our Hospital between 2009 and 2012, who underwent intravenous

thrombolytic treatment. Neurologists, neuroradiologists, and neurosurgeons are on active duty 24h/day and 7 days/week. A stroke code and a specific stroke protocol have been implemented to minimize the time from call to hospital arrival and the door to needle time. The database was prospectively updated and only subjects who had all parameters available were investigated. Intravenous thrombolytic therapy for IS is routinely used in our hospital according to the current international and Italian guidelines [12]. Briefly, patients aged 18 to 80 years, presenting with IS and measurable deficit, were eligible within 4.5 hours from symptom onset after exclusion of ICH. In our setting contraindications to rt-PA infusion are those of the National Institute of Neurological Disorders and Stroke (NINDS) trial [13]. Moreover, patients with an Alberta Stroke Program Early CT Score (ASPECTS) of 7 or less were excluded [14].

Intravenous t-PA was administered at a dose of 0.9 mg per kilogram (maximum, 90 mg), with 10% given as an initial bolus and the remaining 90% as a continuous infusion over a period of 60 minutes.

Neurologic deficit was quantified through the National Institutes of Health Stroke Scale (NIHSS), a 15-item scale, total NIHSS scores ranging from 0 to 42, with higher scores indicating more severe impairment.

We evaluated three month case fatality rate, disability-free survival at 90 days, with freedom from disability defined as a modified Rankin Scale (mRS) of 0 or 1 (no symptoms or no clinically significant disability despite symptoms, respectively), functional independence at three months (mRS < 2), and development of ICH. To monitor this adverse event, CT scans were performed 24 hours and 7 days after treatment. ICH was classified as small or confluent petechiae along the margins of the infarct or within the infarct area without space-occupying effect, as blood clots with space-occupying effect, or as symptomatic ICH when associated with neurological deterioration.

Renal function was evaluated by estimated GFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [15].

Serum creatinine (SCr) assays were performed using the Jaffe method on a Hitachi Modular (Roche Diagnostics, Mannheim, Germany). Renal impairment was defined as GFR<60ml/min/1.73m2 [16].

Statistical Analysis

Data are expressed as absolute numbers, percentage and mean ± standard deviation. Admission NIHSS was also expressed as median and interquartile range. Variables were analyzed using either $\chi 2$, t-test, or Mann-Whitney-U test as appropriate. Analysis was conducted comparing subjects with GFR<60 ml/min/1.73m2 and those with GFR≥60 ml/min/1.73 m2. A two tailed $p < 0.05$ was considered significant. The effect measure of the association ICH and the investigated parameters was the odds ratios (OR) with 95% confidence intervals (95%CIs) calculated by logistic regression analysis. SPSS 13.0 for Windows (SPSS Inc., Chicago, IL, 2004) was used for statistical analysis.

Results

We enrolled 191 stroke patients, with a mean age of 67±12 years of whom 117 had GFR≥60 ml/min/1.73 m2 and 74 GFR<60 ml/min/1.73m2. The demographic and clinical characteristics of the study population are summarized in Table 1. In the 74 patients with

Table 1: Demographic and clinical characteristics of the study population.

	Total population	Patients with GFR ≥ 60 ml/min/1.73m2	Patients with GFR < 60 ml/min/1.73m2	*p*
Number	191	117	74	
Age (years)	67±12	65±13	71±10	< 0.005
Age > 75 ys (n (%))		35 (29.9)	37 (50)	< 0.01
Hypertension (n (%))	99 (51.8)	51 (43.6)	48 (64.9)	< 0.001
Diabetes mellitus (n (%))	43 (22.5)	25 (21.4)	18 (24.3)	NS
Hyperlipidaemia (n (%))	127 (66.5)	76 (65)	51 (69)	NS
Atrial Fibrillation (n (%))	35 (18.3)	25 (21.3)	15 (20.2)	NS
Smoking (n (%))	39 (20.4)	8 (6.8)	31 (41.8)	< 0.001
Systolic blood pressure (mmHg)	147±19	144±18	152±19	< 0.001
Diastolic blood pressure (mmHg)	81±11	80±11	81±12	NS
Serum glucose (mg/dl)	130±52	125±46	138±61	NS
GFR (ml/min/1.73 m2)	69±24	85±16	45±11	< 0.0001
Admission NIHSS **Mean (SD)** **Median (IQR)**	 12±6 11 (7-18)	 12±6 12 (7-18)	 12±6 11 (7-17.5)	NS
Onset to door time (minutes)	78±44	81±46	73±41	NS
Onset to needle time (minutes)	167±44	168±43	165±45	NS

GFR = glomerular filtration rate

Citation: *Fabbian F, Azzini C, Gentile M, De Giorgi A, De Vito A, et al. (2015) Impact of Glomerular Filtration Rate on Intravenous Thrombolytic Therapy in Acute Ischemic Stroke: A Retrospective Study from a Single Italian Center. Arch Clin Nephrol 1(1): 001-006. DOI: http://dx.doi.org/10.17352/acn.000001*

GFR<60 ml/min/1.73m2 the mean GFR was 45±11 ml/min/1.73m2. These patients were older, and had higher prevalence of hypertension and smoking history, as compared to patients with higher GFR. The median NIHSS score at baseline was similar in the two groups (Table 1). Table 2 shows outcome data: three months after the onset of stroke nineteen patients (10%) had died of whom 8 (10.8%) had GFR<60 ml/min/1.73m2. At the same time 56/106 (52.8 %) patients with GFR≥60 ml/min/1.73 m2 and 40/66 (60.6%) subjects with GFR≥60 ml/min/1.73 m2 were alive and free of residual disability (mRS <1). The percentage of patients with minimal disability (mRS <2) was also similar in the two groups. ICH occurred more frequently in patients with GFR<60 ml/min/1.73m2 than in those with GFR≥60 ml/min/1.73 m2 (18.9 vs 7.7 %, p< 0.05). Fatal hemorrhage occurred in 7 patients, 3 with GFR<60 ml/min/1.73m2 and 4 with GFR≥60 ml/min/1.73 m2.

The logistic regression analysis showed that patients with GFR<60 ml/min/1.73m2 had an increased risk of developing ICH (OR = 2.8; 95% CI = 1.14-6.8, p<0.01), the association was still significant after adjusting for age and stroke severity at onset (adjusted OR = 2.5; 95% CI = 1.1-6.2, p<0.05).

Discussion

Although stroke represents a major cause of death and severe disability [17], its impact in the uremic population is still a matter of debate, mainly regarding its treatment.

Cerebrovascular accidents (CVAs) were recorded in 19% of USRDS patients with CKD, with similar prevalence in the different CKD stages [18]. Moreover CVAs were the cause of death in 2.3% of incident dialysis patients in the first 180 days and 3.3% of prevalent dialysis patients [19].

CKD impacts coagulation cascade, platelet function and vessel wall structure [1], and patients on dialysis have been reported to have higher age-adjusted relative risk of stroke as well as hospitalization rates for ICH and IS than the general population [20]. In Japan, it has been reported that ICH had higher prevalence than IS [21], and that more than 70% of the patients with ICH died within 3 months of the onset of symptoms with an incidence of ICH and IS in patients with ESRD of 8.7 and 3.7 per 1000 patient-years, respectively [22]. Recently Gotoh et al. [23] analyzed trends in the incidence of ICH and found that in Japan incidence steeply declined from the 1960s to the 1970s, but that this decline has mitigated since then, probably because of the increased incidence of thalamic hemorrhage in the elderly in recent years.

On the other hand a prospective study on 1041 incident ESRD patients from United States, showed that the overall incidence of CVAs was 4.9 of 100 person-years and IS represented 76% of all events, and cardio embolism accounted for 28% of them [24]. ISs were also more common in a study from United Kingdom in which 2380 patients on hemodialysis were analyzed. Total incidence of stroke was 14.9 of 1000 patient-year whilst IS and ICH incidences were 11.2 and 3.7 of 1000 patient-years respectively [25].

CKD is an independent negative predictor of 30-day survival after acute IS, however data about revascularization are scarce [26].

Whiteley et al. [27] conducted a systematic review and meat-analysis evaluating 55 studies that measured 43 baseline variables in 65264 acute IS patients. Renal impairment was independently associated with post-rt-PA ICH, and their results were similar to ours (OR 2.79 95%CI 1.19-6.54). On the other hand authors could analyze only two studies.

Agrawal et al. [28] evaluated 74 patients who consecutively received intravenous thrombolytic therapy for acute stroke. Twenty seven percent of subjects had GFR<60 ml/min/1.73m2 and were older, with a higher prevalence of diabetes and coronary artery disease than patients with GFR≥60 ml/min/1.73m2. They found no association between CKD and increased ICH, poor functional outcome or death.

Power et al. [29] conducted a retrospective multicenter cohort study between 2009 and 2011, examining 229 stroke patients aged 70 years, treated with alteplase. GFR<60ml/min was independently associated with a statistically significant reduction of the therapeutic effect of alteplase at 24 h, and this persisted at 7 days. However CKD was not associated with a higher rate of ICH.

Chao et al. [30] evaluated 297 patients treated with thrombolytic therapy for IS and classified them into 2 groups on the basis of GFR. ICH was more common in those with GFR<60ml/min/1.73m2, however, multivariate logistic regression did not show any independent association between renal dysfunction and ICH. Moreover, GFR<60ml/min/1.73m2 did not predict functional dependence or death at 1 month and 1 year.

Table 2: Stroke outcome after therapy in the study population.

	Total population	Patients with GFR < 60 ml/min/1.73m2	Patients with GFR ≥ 60 ml/min/1.73m2	*p*
Death 3-month (n (%))	19 (10)	11 (9.4)	8 (10.8)	NS
Survival disability-free (mRS 0-1) (n (%))	96 (55.8)	56 (52.8)	40 (60.6)	NS
Survival with mRS < 2 (n (%))	126 (73.2)	76 (71.7)	50 (75.7)	NS
Intracranial hemorrhage (n (%))	23 (12)	9 (7.7)	14 (18.9)	< 0.05
Petechial (n (%))	5 (2.6)	2 (1.7)	3 (4)	NS
Clot (n (%))	18 (9.4)	7 (6)	11 (14.8)	< 0.05
Symptomatic clots (n (%))	16 (8.4)	6 (5.1)	10 (13.5)	< 0.05
Death for hemorrhage (n (%))	7 (3.7)	3 (2.6)	4 (5.4)	NS

Citation: *Fabbian F, Azzini C, Gentile M, De Giorgi A, De Vito A, et al. (2015) Impact of Glomerular Filtration Rate on Intravenous Thrombolytic Therapy in Acute Ischemic Stroke: A Retrospective Study from a Single Italian Center. Arch Clin Nephrol 1(1): 001-006. DOI: http://dx.doi.org/10.17352/acn.000001*

In 2008 Lyrer et al. [31] evaluated 196 stroke patients treated with intravenous rt-PA. They classified subjects on the basis of mRS. The poor-outcome group was older, had higher NIHSS, glucose levels, C-reactive protein, SCr, and lower GFR. In subjects with lower GFR, causes of death were myocardial infarction, pulmonary embolism, malignant brain infarction, pneumonia, and symptomatic ICH. Every increase in SCr increased the odd for poor outcome.

In Japan, Naganuma et al. [32] conducted a retrospective study in order to evaluate intravenous rt-PA therapy in 578 consecutive stroke patients aged 71 years with a premorbid mRS Score ≤3. CKD was present in 32.2% of cases. These patients were older and more commonly had hypertension, atrial fibrillation, prior ischemic heart disease and prior use of antithrombotic agents than patients without CKD. ICH was more common and median mRS scores at 3 months were higher in patients with CKD than in those without. CKD was independently associated with cerebral poor outcome and mortality.

Tütüncü et al. [33] enrolled 740 subjects of whom 83% had GFR<90ml/min and 5% had GFR<30 ml/min. ICH after intravenous thrombolytic therapy was more frequent in patients with GFR<30ml/min.

Very recently Gensicke et al. [34] conducted an observational study including 4,780 intravenous thrombolysis treated patients, of whom 1,217 (25.5%) had GFR<60mL/min/1.73m2. Patients with low GFR were older, had more stroke severity, more severe hypertension, higher percentage of prior antithrombotics, and were suffering more frequently from hypercholesterolemia and coronary artery disease. A GFR decrease by 10mL/min/1.73m2 increased the risk of death and symptomatic ICH [34].

Finally, CKD did not increase the risk of ICH and poor outcome in a study on 657 IS patients treated with thrombolysis in Taiwan [35].

The majority of the results from the different studies confirm the presence of a negative loop, where patients with CKD are aged and suffer multiple diseases that worsen and are worsened by impaired renal function. Besides it should be taken into account that cigarette smoking, a well-known cardiovascular risk factor, has been reported to be a risk factor for incident CKD, as suggested by a systematic review published in 2007 [36], and in our study subjects with GFR<60ml/min/1.73m2 had higher prevalence of smoking history. Moreover we found that group with GFR<60 ml/min/1.73m2 had higher prevalence of patients aged older than 75 years, and this group was the one with the higher risk of ICH. On the other hand logistic regression analysis showed that the association between GFR<60 ml/min/1.73m2 and ICH was still significant after adjusting for age and stroke severity at onset. It could be that CKD is a biomarker of poor clinical condition [37]. Moreover, adverse drug events have been reported to be more frequent in older adults treated with drugs acting on the cardiovascular system [38]. GFR<60ml/min/1.73m2 is independently associated with subclinical carotid artery damage [39] and in this group of patients brain MRI detected more advanced atherosclerotic changes of the cerebral vessels [40]. Moreover the rate of ICH has been reported to be significantly more frequent in patients with moderate to severe leukoaraiosis of the deep white matter than in patients without relevant leukoaraiosis [41]. On the other hand ICH due to rt-PA could be related to blood-barrier disruption rather than drug accumulation in subjects with reduced renal function, due to the fact that the drugs is mainly metabolized by the liver [11]. Besides, differences among studies could be ascribed not only to the study design, mainly a retrospective one that inevitably involves selection bias, but also to different management of intravenous thrombolytic therapy.

Our study has some limitations. First, the design is retrospective and the study is single-centre evaluating a small number of subjects, therefore selection bias cannot be excluded. Second, GFR<60 ml/min/1.73m2 was correlated with comorbidities therefore we found that subjects with worse clinical condition have a worse outcome, a common finding in medical science. Third, GFR was estimated at the time of admission, hence its measure could had been affected by the acute event. Repeated measures of GFR are needed in order to ascertain the presence of CKD. In fact, CKD categorization may depend on the formula used, as previously demonstrated with different equations [42]. Finally, all patients were treated with regular dose therapy (0.9 mg/kg), without evaluation of GFR, but this is a common clinical practice which may be questioned by studies like ours. Different risk predictors are included in the risk score for ICH in patients with acute IS undergoing intravenous thrombolytic therapy. The GRASPS score [43] includes age, NIHSS systolic blood pressure, blood glucose, ethnicity and gender, whilst the SEDAN score [44] includes glucose level on admission, early infarct sign on admission CT head scan, dense or hyper dense cerebral artery sign on admission CT, age and NIHSS. GFR evaluation is never included in the assessment of hemorrhagic risk. We suggest that evaluation of GFR at hospital admission in subjects with acute IS potentially undergoing intravenous thrombolytic therapy should be considered, because these patients with GFR<60 ml/min/1.73m2 could be at higher risk of hemorrhagic complications.

Conclusion

We found that patients with GFR<60 ml/min/1.73m2 could have an increased risk of ICH after intravenous thrombolysis but the clinical impact of this complication appears to be negligible.

Acknowledgments

This paper is supported (in part) by a scientific institutional grant (Fondo Ateneo Ricerca –FAR), University of Ferrara, Italy.

References

1. Lutz J, Menke J, Sollinger D, Schinzel H, Thürmel K (2014) Haemostasis in chronic kidney disease. Nephrol Dial Transplant 29: 29-40.

2. Fabbian F, Pala M, De Giorgi A, Manfredini F, Mallozzi Menegatti A, et al. (2013) In-hospital mortality in patients with renal dysfunction admitted for myocardial infarction: the Emilia-Romagna region of Italy database of hospital admissions. Int Urol Nephrol 45: 769-775.

3. Chu CY, Su HM, Hsu PC, Lee WH, Lin TH, et al. (2013) Impact of Chronic Kidney Disease in Early Invasive versus Early Conservative Revascularization Strategies in Non-ST-Segment Elevation Acute Coronary Syndromes: A Population-Based Study from NHIRD of Taiwan. Nephron Clin Pract 124: 38-46.

4. Fabbian F, Casetta I, De Giorgi A, Pala M, Tiseo R, et al. (2012) Stroke and

renal dysfunction: are we always conscious of this relationship? Clin Appl Thromb Hemost 18: 305-311.

5. Fabbian F, Gallerani M, Pala M, De Giorgi A, Salmi R, et al. (2014) Association Between In-Hospital Mortality and Renal Dysfunction in 186 219 Patients Hospitalized for Acute Stroke in the Emilia-Romagna Region of Italy. Angiology 65: 906-910.

6. Ovbiagele B (2011) Chronic kidney disease and risk of death during hospitalization for stroke. J Neurol Sci 301: 46-50.

7. De Giorgi A, Fabbian F, Pala M, Tiseo R, Portaluppi F, (2011) Estimation of glomerular filtration rate and assessment of risk of stroke in an emergency setting. Am J Emerg Med 29: 831-832.

8. McCullough PA (2009) Treatment disparities in patients with acute coronary syndromes and kidney disease. Eur Heart J 30: 526-527.

9. Hotchkiss JR, Palevsky PM (2012) Care of the critically ill patient with advanced chronic kidney disease or end-stage renal disease. Curr Opin Crit Care 18: 599-606.

10. Donnan GA, Davis SM, Parsons MW, Ma H, Dewey HM, (2011) How to make better use of thrombolytic therapy in acute ischemic stroke. Nat Rev Neurol 7: 400-409.

11. Acheampong P, Ford GA (2012). Pharmacokinetics of alteplase in the treatment of ischaemic stroke. Expert Opin Drug Metab Toxicol 8: 271-281.

12. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, et al. (2013) Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke 44: 870-947.

13. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group (1995) Tissue Plasminogen Activator for Acute Ischemic Stroke. N Engl J Med 333: 1581-1587.

14. Barber PA, Demchuk AM, Zhang J, Buchan AM (2000) Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. Lancet 355: 1670-1674.

15. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, et al. (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150: 604-612.

16. National Kidney Foundation (2002). K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 39: S1-266.

17. Guccione AA, Felson DT, Anderson JJ, Anthony JM, Zhang Y, et al. (1994) The effect of specific medical conditions on the functional limitations of elders in the Framingham study. Am J Public Health 84: 351-358.

18. USRDS 2012 annual data report (2013) cardiovascular disease in patients with CKD. Am J Kidney Dis 61: 78-82.

19. USRDS 2012 annual data report (2013) Cardiovascular disease. Am J Kidney Dis; 61: 250-258.

20. Seliger SL, Gillen DL, Longstreth WT Jr, Kestenbaum B, Stehman-Breen CO (2003). Elevated risk of stroke among patients with end-stage renal disease. Kidney Int 64: 603-609.

21. Iseki K, Fukiyama K, Okawa Dialysis Study (OKIDS) Group (2000) Clinical demographics and long-term prognosis after stroke in patients on chronic haemodialysis. The Okinawa Dialysis Study (OKIDS) Group. Nephrol Dial Transplant 15: 1808-1813.

22. Kawamura M, Fijimoto S, Hisanaga S, Yamamoto Y, Eto T (1998). Incidence, outcome, and risk factors of cerebrovascular events in patients undergoing maintenance hemodialysis. Am J Kidney Dis 31: 991-996.

23. Gotoh S, Hata J, Ninomiya T, Hirakawa Y, Nagata M, et al. (2014) Trends in the incidence and survival of intracerebral hemorrhage by its location in a Japanese community. Circ J 78: 403-409.

24. Sozio SM, Armstrong PA, Coresh J, Jaar BG, Fink NE, et al. (2009) Cerebrovascular disease incidence, characteristics, and outcomes in patients initiating dialysis: the choices for healthy outcomes in caring for ESRD (CHOICE) study. Am J Kidney Dis 54: 468-477.

25. Power A, Chan K, Singh SK, Taube D, Duncan N (2012) Appraising stroke risk in maintenance hemodialysis patients: a large single-center cohort study. Am J Kidney Dis 59: 249-257.

26. Brzosko S, Szkolka T, Mysliwiec M (2009) Kidney disease is a negative predictor of 30-day survival after acute ischaemic stroke. Nephron Clin Pract 112: c79-c85.

27. Whiteley WN, Slot KB, Fernandes P, Sandercock P, Wardlaw J (2012) Risk factors for intracranial hemorrhage in acute ischemic stroke patients treated with recombinant tissue plasminogen activator: a systematic review and meta-analysis of 55 studies. Stroke 43: 2904-2909.

28. Agrawal V, Rai B, Fellows J, McCullough PA (2010) In-hospital outcomes with thrombolytic therapy in patients with renal dysfunction presenting with acute ischaemic stroke. Nephrol Dial Transplant 25: 1150-1157.

29. Power A, Epstein D, Cohen D, Bathula R, Devine J, et al. (2013) Renal impairment reduces the efficacy of thrombolytic therapy in acute ischemic stroke. Cerebrovasc Dis 35: 45-52.

30. Chao TH, Lin TC, Shieh Y, Chang TY, Hung KL, et al. (2013) Intracerebral Hemorrhage after Thrombolytic Therapy in Acute IS Patients with Renal Dysfunction. Eur Neurol 70: 316-321.

31. Lyrer PA, Fluri F, Gisler D, Papa S, Hatz F, et al. (2008) Renal function and outcome among stroke patients treated with IV thrombolysis. Neurology 71: 1548-1550.

32. Naganuma M, Koga M, Shiokawa Y, Nakagawara J, Furui E, et al. (2011) Reduced estimated glomerular filtration rate is associated with stroke outcome after intravenous rt-PA: the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement (SAMURAI) rt-PA registry. Cerebrovasc Dis 31: 123-129.

33. Tütüncü S, Ziegler AM, Scheitz JF, Slowinski T, Rocco A, et al. (2013) Severe renal impairment is associated with symptomatic intracerebral hemorrhage after thrombolysis for ischemic stroke. Stroke 44: 3217-3219.

34. Gensicke H, Zinkstok SM, Roos YB, Seiffge DJ, Ringleb P, et al. (2013) IV thrombolysis and renal function. Neurology 81: 1780-1788.

35. Hsieh CY, Lin HL, Hsieh HC, Lai ECC, Chen CH (2014) Is renal dysfunction associated with adverse stroke outcome after thrombolytic therapy? Cerebrovasc Dis 37: 51-56.

36. Jones-Burton C, Seliger SL, Scherer RW, Mishra SI, Vessal G, et al. (2007) Cigarette Smoking and Incident Chronic Kidney Disease: A Systematic Review. Am J Nephrol 27: 342-351.

37. Smyth A, Glynn LG, Murphy AW, Mulqueen J, Canavan M, et al. (2013) Mild chronic kidney disease and functional impairment in community-dwelling older adults. Age Ageing 42: 488-494.

38. Marcum ZA, Fried LF (2011) Aging and antihypertensive medication-related complications in the chronic disease patient. Curr Opin Nephrol Hypertens 20: 449-456.

39. Lu B, Wan J, Yang Y, Li Y, Hu R (2013) The estimated glomerular filtration rate is associated with subclinical atherosclerosis, independently of albuminuria, in patients with type 2 diabetes. International Angiology 32: 532-539.

40. Ueda K, Watanabe Y, Katsumata T, Kaneko T, Otori T, et al. (2011). Carotid intima-media thickness and cerebral white matter lesions are more advanced in acute ischemic stroke patients with renal dysfunction. Clin Nephrol 76: 290-295.

41. Neumann-Haefelin T, Hoelig S, Berkefeld J, Fiehler J, Gass A, et al. (2006). Leukoaraiosis is a risk factor for symptomatic intracerebral hemorrhage after thrombolysis for acute stroke. Stroke 37: 2463-2466.

42. Fabbian F, Pala M, Monesi M, De Giorgi A, Mallozzi Menegatti A, et al. (2013). The estimation of glomerular filtration rate in type 2 diabetic patients

may depend on the equation used. Eur Rev Med Pharmacol Sci 17: 2791-2797.

43. Menon BK, Saver JL, Prabhakaran S, Reeves M, Liang L, et al. (2012). Risk score for intracranial hemorrhage in patients with acute IS treated with intravenous tissue-type plasminogen activator. Stroke 43: 2293-2299.

44. Strbian D, Engelter S, Michel P, Meretoja A, Sekoranja L, et al. (2012) Symptomatic intracranial hemorrhage after stroke thrombolysis: the SEDAN score. Ann Neurol 71: 634-41.