IV thrombolysis and renal function

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ABSTRACT

Objective: To investigate the association of renal impairment on functional outcome and complications in stroke patients treated with IV thrombolysis (IVT).

Methods: In this observational study, we compared the estimated glomerular filtration rate (GFR) with poor 3-month outcome (modified Rankin Scale scores 3–6), death, and symptomatic intracranial hemorrhage (sICH) based on the criteria of the European Cooperative Acute Stroke Study II trial. Unadjusted and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Patients without IVT treatment served as a comparison group.

Results: Among 4,780 IVT-treated patients, 1,217 (25.5%) had a low GFR (<60 mL/min/1.73 m^2). A GFR decrease by 10 mL/min/1.73 m^2 increased the risk of poor outcome (OR [95% CI]): ($OR_{unadjusted}$ 1.20 [1.17–1.24]; $OR_{adjusted}$ 1.05 [1.01–1.09]), death ($OR_{unadjusted}$ 1.33 [1.28–1.38]; $OR_{adjusted}$ 1.18 [1.11–1.249]), and sICH ($OR_{unadjusted}$ 1.15 [1.01–1.22]; $OR_{adjusted}$ 1.11 [1.04–1.20]). Low GFR was independently associated with poor 3-month outcome ($OR_{adjusted}$ 1.32 [1.10–1.58]), death ($OR_{adjusted}$ 1.73 [1.39–2.14]), and sICH ($OR_{adjusted}$ 1.64 [1.21–2.23]) compared with normal GFR (60–120 mL/min/1.73 m^2). Low GFR ($OR_{adjusted}$ 1.64 [1.21–2.23]) and stroke severity ($OR_{adjusted}$ 1.05 [1.03–1.07]) independently determined sICH. Compared with patients who did not receive IVT, treatment with IVT in patients with low GFR was associated with poor outcome ($OR_{adjusted}$ 1.79 [1.41–2.25]), and with favorable outcome in those with normal GFR ($OR_{adjusted}$ 0.77 [0.63–0.94]).

Conclusion: Renal function significantly modified outcome and complication rates in IVT-treated stroke patients. Lower GFR might be a better risk indicator for sICH than age. A decrease of GFR by 10 mL/min/1.73 m^2 seems to have a similar impact on the risk of death or sICH as a 1-point-higher NIH Stroke Scale score measuring stroke severity. *Neurology*® 2013;81:1780–1788

GLOSSARY

CI = confidence interval; **CKD-EPI** = Chronic Kidney Disease Epidemiology Collaboration; **ECASS** = European Cooperative Acute Stroke Study; **GFR** = glomerular filtration rate; **ICH** = intracranial hemorrhage; **IVT** = IV thrombolysis; **MDRD** = Modification of Diet in Renal Disease; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **NINDS** = National Institute of Neurological Disorders and Stroke; **OR** = odds ratio; **SCr** = serum creatinine; **sICH** = symptomatic intracranial hemorrhage.

Renal dysfunction is associated with higher mortality in stroke patients[1–6] and with an increased risk of ischemic and hemorrhagic stroke in the general population.[7,8] In stroke patients treated with IV thrombolysis (IVT), the impact of renal function on outcome or complications remains to be clarified. In 3 studies, impaired kidney function was associated with unfavorable 3-month outcome,[9–11] but not in a fourth one.[12] Furthermore, renal dysfunction was reported to be a risk factor for symptomatic intracranial hemorrhage (sICH) as a complication of IVT in one study,[10] but this finding could not be confirmed by others.[9,11,12] Interestingly, renal hyperfiltration was reportedly associated with increased mortality according to 2 recent reports in stroke patients in general.[2,4] It remains unclear whether this association holds true for IVT-treated patients.

Supplemental data at www.neurology.org

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Using pooled individual data from 4,780 patients treated with IVT, we studied whether impaired renal function regarding low or high glomerular filtration rate (GFR) was independently associated with functional 3-month outcome and increased risk of sICH, and we aimed to provide quantitative estimates for these associations. Second, we studied whether high GFR (renal hyperfiltration) was associated with worse functional outcome or increased frequency of intracranial hemorrhage (ICH). Third, we added a cohort of 1,427 stroke patients treated without IVT to assess the interaction between renal insufficiency and IVT treatment.

METHODS As a joint initiative of 11 European stroke centers, we designed a large collaborative cohort study to address several important IVT-related clinical research questions. In this study, we investigated the impact of renal function on outcomes of stroke patients receiving IVT. All participating centers treated patients with acute ischemic stroke with IVT according to current guidelines (http://www.eso-stroke.org/recommendations.php?cid=9).

Data from individual patients were collected with a standardized form with predefined variables as it was used in previous studies.[13,14] Local study investigators completed the forms systematically using prospectively ascertained in-hospital IV ischemic stroke thrombolysis registries. Completed forms from all centers were compiled in the coordinating center Basel, where the analysis of the pooled data was performed, as described previously.[13,14]

The following prospectively ascertained variables were used: age, sex, initial stroke severity as assessed using the NIH Stroke Scale (NIHSS),[15] blood pressure before IVT, onset to treatment, initial serum creatinine (SCr) and glucose values in blood serum, etiology according to the TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria,[16] and vascular risk factors according to predefined criteria.[17] Post hoc, we added prior treatment with antithrombotic agents (antiplatelet agents and anticoagulants). Functional outcome was assessed by outpatient visits or telephone calls using the modified Rankin Scale (mRS) at 3 months. There was monitoring for ICH by follow-up CT or MRI as done in prior research.[14]

Each center reported on the period for which they had prospectively collected data on consecutive patients up to December 31, 2011 (table e-1 on the *Neurology*® Web site at www.neurology.org). Patients were excluded if 1) they had a final diagnosis other than acute ischemic stroke (i.e., patients with stroke mimics),[18] 2) their SCr values were not available, or 3) 3-month outcome data were not available.

Primary outcome measures were poor functional 3-month outcome, defined as mRS scores 3 to 6, death, and sICH according to criteria of the European Cooperative Acute Stroke Study II (ECASS-II) trial ($sICH_{ECASS\text{-}II}$).[19] Secondary outcome measures were unfavorable outcome (mRS scores 2–6), and ICH according to other definitions: all ICH (ICH_{ALL}), sICH based on the criteria of the National Institute of Neurological Disorders and Stroke trial ($sICH_{NINDS}$), and fatal ICH ($sICH_{FATAL}$).[20]

GFR as a measure of renal function was calculated applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation: $GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{age}$ (if female and SCr $\leq$0.7 mg/dL), $GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{age}$ (if female and SCr $\geq$0.7 mg/dL), $GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{age}$ (if male and SCr $\leq$0.9 mg/dL), and $GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{age}$ (if male and SCr $\geq$0.9 mg/dL).[21]

In addition, we assessed the interaction of renal insufficiency and IVT treatment between patients treated with and without IVT. A total of 1,427 patients without IVT treatment admitted to hospital within 6 hours after symptom onset were included in the analysis. Data were collected from 3 stroke registries (Lausanne between January 1, 2003 and December 31, 2012; Brescia between April 2007 and February 2010; and Bernese between January 1, 2004 and June 30, 2011).[22–24]

Post hoc, in a subset of patients, data of early hypodensity on initial CT scan (present vs absent) and data of recanalization (partial/complete vs no recanalization of the main intracranial cerebral artery) were included in subgroup analyses. These were restricted to patients from centers routinely collecting such data (i.e., Basel and Lausanne).

Standard protocol approvals, registrations, and patient consents. The study was approved by the ethics committee in Basel, Switzerland. The requirement for additional local ethical approval differed among participating centers and was obtained if required.

Statistical analyses. Statistical analysis was performed using SPSS (version 19.0 for Windows; SPSS Inc., Chicago, IL). Renal function as quantified by the GFR was compared with outcome measures as a continuous variable and as a categorical variable. For the latter, patients' GFRs were divided into 3 groups using thresholds reported in prior research[4]: 1) low GFR $<$60 mL/min/1.73 m^2, 2) normal GFR 60 to 120 mL/min/1.73 m^2, and 3) high GFR $>$120 mL/min/1.73 m^2. Post hoc, we added a category very low GFR defined as $<$30 mL/min/1.73 m^2. Data were summarized as median ($\pm$ interquartile range). Normal GFR served as the reference group. We compared demographic and clinical baseline characteristics among patients in the 3 GFR groups using Fisher exact test or the χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables. The association between GFR (both as a continuous variable and as a categorical variable as defined above) and each outcome was estimated by calculating the odds ratios (ORs) with 95% confidence intervals (CIs) using binary logistic regression models. In the multivariate analysis, the models were adjusted for all variables with p value $<$0.1 in the univariate analyses. The adjustments in the models comparing "high GFR" with "normal GFR" as well as "IVT" with "non-IVT" were restricted to "age" and "NIHSS score"—to avoid overfitting in a small sample size.

In addition, we rendered analyses focusing on the shape of the relation between the probability of the primary outcome measures and GFR further including sex, age, and NIHSS score as covariates. For GFR and numerical covariates (i.e., age and NIHSS score), linear, quadratic, and cubic terms were considered a priori, but models were then simplified by successively eliminating highest order terms, which increased the Bayesian information criterion. The information criteria were applied to derive a parsimonious final model (minimizing the Bayesian information criterion).

RESULTS **IVT population: Baseline characteristics and regression analyses.** Data were suitable for analysis in 4,780 (97.2%) of the 4,916 IVT-treated patients included in the entire database; 48 patients lacking creatinine values and 88 patients with missing 3-month outcome data were excluded from the present analysis. Among eligible patients, 1,217 (25.5%) had low GFR, 3,504 (73.3%) a normal GFR, and 59 (1.2%) a high

GFR. Baseline characteristics and number of outcome events are presented in table 1. Patients with low GFR were a median of 10 years older, were more likely to be female, had a higher NIHSS score, and had more vascular risk factors than patients with normal GFR. More patients with low GFR had large-artery atherosclerosis as underlying stroke etiology than patients with normal GFR. In contrast, patients with high GFR were on average 33 years younger, had a lower median NIHSS score, and had fewer risk factors than patients with normal GFR (table 1).

All outcome events occurred significantly more often in the low GFR group than in the normal GFR group. Patients in the high GFR group had a better outcome at 3 months, but did not otherwise significantly differ from the normal GFR group. The distribution of the unadjusted 3-month outcome and the frequency of $sICH_{ECASS\text{-}II}$ stratified to the 3 GFR groups are presented in figure 1.

In univariate analyses, decreasing GFR (by 10 mL/min/1.73 m^2) and low GFR were significantly associated with all primary and all secondary outcome measures (tables 2 and e-2). High GFR was associated with a lower frequency of poor outcomes (27.1% vs 40.7%, $p = 0.044$) and a trend toward a lower frequency of unfavorable outcomes (45.8% vs 58.0%, $p = 0.064$) compared to patients with normal GFR. High GFR was neither associated with death nor ICH in all categories (tables 2 and e-2).

After adjustment for age, sex, stroke severity (NIHSS score), blood glucose concentration, systolic blood pressure, atrial fibrillation, onset to treatment, hypertension, diabetes, hypercholesterolemia, smoking, coronary artery disease, prior stroke, and prior treatment with antithrombotics, every decrease of GFR by 10 mL/min/1.73 m^2 increased the risk of poor outcome ($OR_{adjusted}$ 1.05, 95% CI 1.01–1.09, $p = 0.017$), death ($OR_{adjusted}$ 1.18, 95% CI 1.11–1.24, $p < 0.001$), and $sICH_{ECASS\text{-}II}$ ($OR_{adjusted}$ 1.11, 95% CI 1.04–1.20, $p = 0.003$). After adjustment for the aforementioned variables, low GFR was still associated with poor outcome ($OR_{adjusted}$ 1.32, 95% CI 1.10–1.58, $p = 0.003$) and death ($OR_{adjusted}$ 1.73, 95% CI 1.39–2.14, $p < 0.0001$). Interestingly, for $sICH_{ECASS\text{-}II}$, stroke severity ($OR_{adjusted}$ 1.05, 95% CI 1.03–1.07, $p < 0.001$) and low GFR ($OR_{adjusted}$ 1.64, 95% CI 1.21–2.23, $p = 0.001$) were the only independent determinants, while all other covariates including age had no significant impact.

Post hoc analysis revealed that in patients with very low GFR vs normal GFR, the odds for poor outcome and for death were higher than for low GFR (table 3). For high GFR, after adjustment for age and stroke severity, there was no longer an association with functional outcome measures (tables 3 and e-3). Based on a parsimonious final model, figure e-1 shows an almost linear association between decreasing GFR with increasing risk of "poor outcome" and "death," adjusted for age, sex, and NIHSS score.

IVT population: Subgroup analyses. In a subset of patients (n = 942 from Basel and Lausanne), data of early hypodensity on initial CT scan and recanalization were available. Patients with early hypodensity on initial CT scan were at significantly increased risk of poor outcome ($OR_{unadjusted}$ 2.48, 95% CI 1.88–3.23, $p < 0.001$), death ($OR_{unadjusted}$ 2.24, 95% CI 1.55–3.23, $p < 0.001$), and $sICH_{ECASS\text{-}II}$ ($OR_{unadjusted}$ 2.30, 95% CI 1.15–4.56, $p = 0.018$). After adjustment for renal function, both low GFR and presence of early hypodensity on initial CT had significant impact on all primary outcome events.

Low GFR did not modify recanalization rates in patients with initial occlusion of a main intracranial artery ($OR_{unadjusted}$ 0.95, 95% CI 0.61–1.47, $p = 0.803$). Female sex ($OR_{unadjusted}$ 0.48, 95% CI 0.32–0.72, $p < 0.001$), lower NIHSS score (each point) at stroke onset ($OR_{unadjusted}$ 0.96, 95% CI 0.93–0.99, $p = 0.008$), and absence of early hypodensity on initial CT ($OR_{unadjusted}$ 0.61, 95% CI 0.41–0.92, $p = 0.019$) were determinants of partial or complete recanalization after IVT.

IVT-treated compared with non–IVT-treated patients. In the non-IVT group, 1,427 patients were eligible for analysis. Comparison of baseline characteristics between patients treated with and without IVT is presented in table 1. IVT-treated patients had more severe strokes than patients in the non-IVT group. Median age and onset-to-treatment or onset-to-door time did not differ significantly between the 2 groups.

IVT-treated patients with normal GFR had lower risk of a poor 3-month outcome ($OR_{adjusted}$ 0.77, 95% CI 0.63–0.94, $p = 0.010$) or death ($OR_{adjusted}$ 0.71, 95% CI 0.54–0.95, $p = 0.020$) than patients not treated with IVT. In patients with low GFR, the odds for poor outcome ($OR_{adjusted}$ 1.79, 95% CI 1.41–2.25, $p < 0.001$) or death ($OR_{adjusted}$ 1.51, 95% CI 1.15–1.98, $p = 0.003$) were higher in the IVT than in the non-IVT group. Compared with the non-IVT group, the risk of $sICH_{ECASS\text{-}II}$ was higher in IVT-treated patients with normal GFR ($OR_{adjusted}$ 5.31, 95% CI 2.33–12.12, $p < 0.001$) and with low GFR ($OR_{adjusted}$ 21.25, 95% CI 4.85–99.03, $p < 0.001$).

DISCUSSION This cohort study, the largest thus far to investigate the impact of renal function in IVT-treated stroke patients, revealed the following main findings: 1) GFR as a continuous or categorical variable was a determinant of outcome and complications in IVT; 2) impaired renal function (i.e., GFR <60 mL/min/1.73 m^2) independently predicted poor functional outcome, death, and sICH; 3) high

Table 1 Clinical characteristics of IVT-treated and non-IVT-treated stroke patients stratified to low and high vs normal GFR (reference group) and in comparison between treatment groups

Baseline characteristics		All		Low GFR		High GFR		Normal GFR compared with:		
IVT treatment		n = 4,780		n = 1,217		n = 59		n = 3,504		
Non-IVT treatment		n = 1,427		n = 465		n = 17		n = 946	Low GFR	High GFR
	Group		*p* Value		*p* Value		*p* Value		*p* Value	*p* Value
Age, y, median (IQR)	IVT	71 (60-79)	0.059	78 (72-83)	0.003	35 (24-54)	0.529	68 (57-76)	<0.001	<0.001
	Non-IVT	72 (59-80)		80 (74-85)		30 (25-45)		66 (56-76)	<0.001	<0.001
Men, n (%)	IVT	2,657 (55.6)	<0.001	517 (42.5)	0.001	33 (55.9)	0.835	2,106 (60.1)	<0.001	0.514
	Non-IVT	882 (61.8)		241 (51.8)		10 (58.8)		631 (66.7)	<0.001	<0.001
Stroke severity, NIHSS score, median (IQR)	IVT	11 (7-17)	<0.001	12 (8-18)	<0.001	10 (7-17)	<0.001	11 (6-16)	<0.001	0.887
	Non-IVT	4 (2-10)		6 (3-14)		3 (2-6)		4 (2-8)	<0.001	0.333
Systolic blood pressure, mm Hg, median (IQR)	IVT	154 (140-171)	0.420	158 (140-176)	0.512	130 (120-149)	0.381	154 (139-170)	<0.001	<0.001
	Non-IVT	153 (135-172)		159 (141-180)		131 (126-151)		151 (135-170)	<0.001	0.010
Onset to treatment (or to door), min, median (IQR)	IVT	140 (105-177)	0.096	140 (105-175)	0.022	134 (106-170)	0.008	140 (105-178)	0.855	0.454
	Non-IVT	135 (77-220)		128 (73-208)		188 (134-235)		137 (78-226)	0.139	0.129
Creatinine on admission, μmol/L, median (IQR)	IVT	81 (68-97)	<0.001	111 (96-131)	0.001	50 (36-62)	0.206	74 (64-86)	<0.001	<0.001
	Non-IVT	86 (71-105)		116 (101-134)		51 (47-61)		77 (68-88)	<0.001	<0.001
Glucose on admission, mg/dL, median (IQR)	IVT	6.7 (5.8-8.0)	<0.001	7.0 (6.0-8.7)	<0.001	5.8 (5.2-6.7)	0.904	6.5 (5.7-7.8)	<0.001	0.001
	Non-IVT	6.4 (5.6-7.7)		6.5 (5.7-8.0)		5.8 (5.3-6.3)		6.4 (5.5-7.6)	0.039	0.076
Prior antithrombotics, n (%)	IVT	2,076 (43.4)	<0.001	721 (59.1)	0.005	11 (18.4)	0.002	1,344 (38.4)	<0.001	0.002
	Non-IVT	776 (54.3)		308 (66.2)		9 (52.9)		459 (48.5)	<0.001	<0.001
Atrial fibrillation, n (%)	IVT	1,318 (27.8)	<0.001	480 (39.7)	0.132	9 (15.5)	0.095	829 (23.9)	<0.001	0.162
	Non-IVT	258 (18.1)		137 (29.5)		1 (5.9)		121 (12.8)	<0.001	0.097
Hypertension, n (%)	IVT	3,169 (66.5)	0.472	985 (81.0)	0.513	13 (22.0)	0.70	2,171 (62.2)	<0.001	<0.001
	Non-IVT	829 (58.1)		343 (73.8)		3 (17.6)		483 (51.1)	<0.001	0.001
Smoking, n (%)	IVT	970 (21.3)	0.037	117 (10.3)	0.278	22 (38.6)	0.752	831 (24.7)	<0.001	0.017
	Non-IVT	280 (19.6)		44 (9.5)		7 (41.2)		229 (24.2)	<0.001	0.218
Hypercholesterolemia, n (%)	IVT	1,657 (37.4)	<0.001	443 (40.9)	<0.001	9 (15.5)	0.836	1,205 (36.6)	<0.001	0.001
	Non-IVT	530 (37.1)		199 (42.8)		2 (11.8)		329 (34.8)	0.005	0.008
Diabetes mellitus, n (%)	IVT	891 (18.7)	0.059	301 (24.8)	0.572	5 (8.5)	0.234	585 (16.8)	0.011	0.111
	Non-IVT	212 (14.8)		97 (20.9)		1 (5.9)		115 (12.2)	<0.001	0.117
Coronary artery disease, n (%)	IVT	830 (17.4)	0.243	319 (26.3)	0.035	4 (6.8)	0.897	507 (14.5)	<0.001	0.131
	Non-IVT	211 (14.8)		89 (19.1)		1 (5.9)		121 (12.8)	0.001	0.346

Continued

Table 1 Continued

Baseline characteristics		All		Low GFR		High GFR		Normal GFR compared with:			
IVT treatment		n = 4,780		n = 1,217		n = 59		n = 3,504			
Non-IVT treatment		n = 1,427		n = 465		n = 17		n = 946		Low GFR	High GFR
	Group		p Value		p Value		p Value		p Value		p Value
Prior stroke, n (%)[a]	IVT	616 (12.9)	—	214 (17.6)	—	3 (5.1)	—	399 (11.4)		<0.001	0.149

Abbreviations: GFR = glomerular filtration rate; IQR = interquartile range; IVT = IV thrombolysis; NIHSS = NIH Stroke Scale. Low GFR <60 mL/min/1.73 m^2; high GFR >120 mL/min/1.73 m^2.

[a] Not available in the non-IVT group.

GFR (>120 mL/min/1.73 m^2) was neither associated with poor functional outcome nor with death or sICH; and 4) in contrast to patients with normal GFR, patients with renal impairment received no beneficial effect with IVT treatment compared with nonthrombolyzed patients.

The impact of renal function on functional outcome and hemorrhagic complications in IVT-treated patients had not been satisfactorily investigated. We are aware of solely 4 studies addressing these points, with inconsistent results. These discrepancies may be attributable to the relatively small sample sizes (n = 74, 196, 229, and 578 patients).[9–12] Renal impairment independently predicted poor functional outcome in 3 studies[9–11] and death in 2 studies.[9,10] A fourth study could not confirm these findings.[12] Furthermore, in one study, sICH occurred significantly more often in patients with low GFR,[10] whereas 3 other studies could not find such an association.[9,11,12]

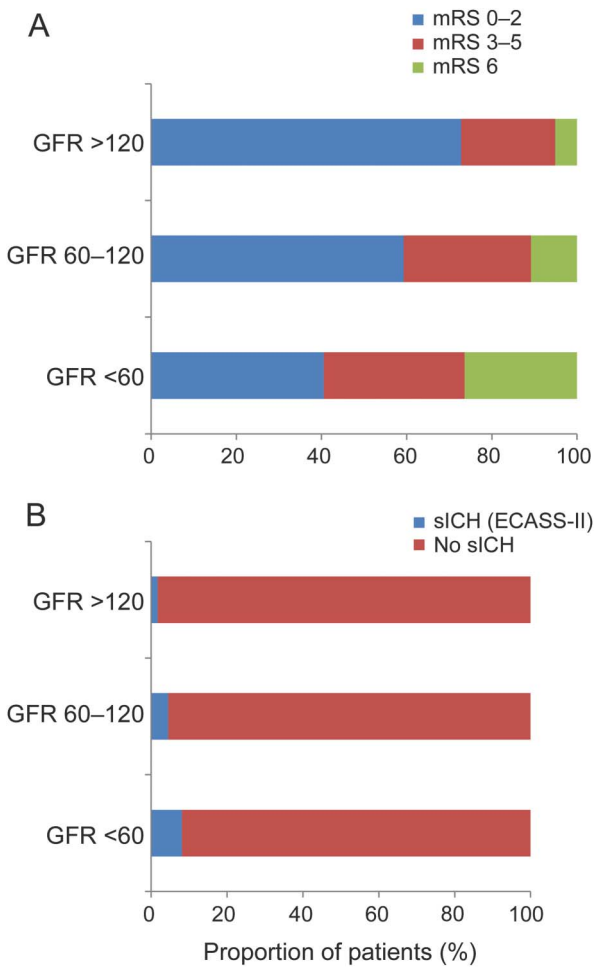
This large multicenter study with 4,780 IVT-treated patients had the power to address this lack of information: renal function is a strong predictor for poor functional outcome, death, and sICH. In patients with GFR <60 mL/min/1.73 m^2, the risk of poor functional outcome (mRS scores 3–6) increased by 34% at 3 months compared with patients with normal GFR (GFR 60–120 mL/min/1.73 m^2). The risk of death increased by at least 39% and may even reach 114% (i.e., 95% CI). Symptomatic ICH—according to the ECASS-II and NINDS criteria—occurred 1.7- and 1.4-fold more frequently.

A decrease in GFR by 10 mL/min/1.73 m^2 had at least the same predictive value as a 1-point change in the NIHSS for death and sICH. These results show that impaired renal function significantly modified outcome and complication rates in patients treated with IVT and should therefore be considered in future IVT studies and registries.

Interestingly, age did not independently predict the risk of sICH as low GFR and stroke severity were the only independent covariates. This unexpected observation might be explained by the fact that estimation of the GFR by the CKD-EPI formula contains the variable age. Alternatively, lower GFR might be a better indicator for impaired health status than higher age. In addition, antithrombotics, although more often used in patients with renal impairment, did not independently influence the risk of sICH.

Regarding possible explanations of our key findings, renal dysfunction was a major risk factor for cardiovascular complications after a myocardial infarction[25]; in analogy to these findings, putative mechanisms by which renal dysfunction affects outcome and complications in IVT-treated patients may include renal anemia, oxidative stress, inflammation,

Figure 1 GFR-depending proportion of patients with (A) unadjusted 3-month outcome, and (B) occurrence of sICH



ECASS = European Cooperative Acute Stroke Study; GFR = glomerular filtration rate; mRS = modified Rankin Scale; sICH = symptomatic intracranial hemorrhage.

endothelial dysfunction, and paradoxical effects on hemostasis (i.e., bleeding and thrombosis).[25,26]

As another novel aspect, we investigated the impact of renal hyperfiltration (>120 mL/min/1.73 m^2) on outcome in IVT-treated patients. Previously, hyperfiltration was associated with a higher mortality rate in general patients (i.e., not an IVT-treated stroke population) at 30 days, and at long-term follow-up in 2 studies.[2,4] We found no increased risk of poor functional outcome, death, or sICH in patients with hyperfiltration. In turn, in the univariate analysis, hyperfiltration was associated with a lower chance of a poor outcome, which however disappeared after adjustment for age and stroke severity. The number of patients with hyperfiltration in the 2 studies was 54 and 106, but their proportion was higher (4.6% and 11.1%) than in our study (1.2%). These differences might be attributable to variations in the studied stroke populations (e.g., age distribution, IVT treatment) or methodologic differences such as the formula used to estimate GFR (i.e., Modification of Diet in Renal Disease [MDRD][2,4] and CKD-EPI in our study). The MDRD formula was developed by studying patients with CKD and was criticized as being inaccurate at higher GFR values.[21] Recently, the CKD-EPI formula predicted clinical risk more accurately than the MDRD formula across a broad spectrum of patients, including patients with higher GFR values.[27]

To clarify whether patients with impaired renal function still benefit from IVT, we included in the analysis a group of stroke patients not treated with IVT, who were admitted to the hospital within 6 hours after stroke onset. As expected, the control group had a marked lower median NIHSS score at stroke onset (4 vs 11), but the onset-to-treatment or onset-to-door time did not differ significantly.

Our post hoc nonrandomized comparison with a cohort of patients treated without IVT revealed that patients with normal GFR benefited from IVT treatment. The reduction in odds of poor outcome was similar to a meta-analysis of 6 randomized controlled IVT trials (OR 0.80, 95% CI 0.69–0.93, $p = 0.003$ vs OR 0.77, 95% CI 0.63–0.94, $p = 0.010$).[28]

In contrast, patients with renal impairment did not benefit from IVT treatment. One explanation could be that patients with renal insufficiency have reduced fibrinolysis rates, due to less clot permeability and higher clot rigidity.[29,30] However, in our subgroup of IVT-treated patients with initial occlusion of a main intracranial artery, renal function had no impact on recanalization rates. Because of methodologic limitations, we urge cautious interpretation of these findings.

Strengths of this study include 1) the large sample size addressing the impact of renal function on outcome in IVT-treated patients, which reduces the odds for false-positive or -negative findings and allowed corrections for several confounding variables; 2) the systematic and standardized assessment of data collection with only a few missing data (2.77%); and 3) the inclusion of non–IVT-treated patients as a comparison group.

Nevertheless, we are aware of the following limitations. First, data came from registries that were not monitored, and the cohorts (IVT vs non-IVT groups) differed in baseline characteristics and were nonrandomized. Because observational nonrandomized studies have a higher risk of bias, we urge a cautious interpretation of these comparisons. Second, even if the new CKD-EPI formula has a higher accuracy than the MDRD formula, neither has been validated in the elderly so far.[3,27] Furthermore, we did not correct for race, and information about the cause of renal insufficiency was not available. Third, although we included factors associated with both renal impairment and outcome in the multivariate analysis, it is possible that these adjustments were not complete.

Table 2 Univariate analysis of clinical characteristics in patients treated with IVT

Predictor for	Poor outcome (mRS 3–6)	Death	$sICH_{ECASS-II}$
Age (each year)	1.05 (1.04–1.05)[a]	1.07 (1.06–1.08)[a]	1.02 (1.01–1.03)[a]
Sex	1.53 (1.37–1.72)[a]	1.36 (1.16–1.60)[a]	1.09 (0.85–1.41)
NIHSS (each point)	1.19 (1.18–1.20)[a]	1.15 (1.14–1.17)[a]	1.06 (1.04–1.08)[a]
Glucose (each mg/dL)	1.12 (1.01–1.15)[a]	1.11 (1.08–1.14)[a]	1.06 (1.01–1.10)[a]
Systolic blood pressure (each mm Hg)	1.004 (1.002–1.007)[a]	1.006 (1.003–1.010)[a]	1.00 (0.99–1.01)
Onset to treatment (each minute)	1.001 (1.000–1.002)[b]	1.000 (0.999–1.001)	1.000 (0.998–1.002)
Atrial fibrillation	1.96 (1.72–2.23)[a]	1.97 (1.67–2.33)[a]	1.49 (1.14–1.94)[a]
Diabetes mellitus	1.62 (1.40–1.88)[a]	1.66 (1.38–2.00)[a]	1.54 (1.15–2.07)[a]
Hypertension	1.49 (1.32–1.68)[a]	1.77 (1.47–2.13)[a]	1.75 (1.30–2.36)[a]
Hypercholesterolemia	0.78 (0.70–0.90)[a]	0.82 (0.68–0.97)[a]	1.09 (0.83–1.42)
Current smoking	0.75 (0.66–0.86)[a]	0.57 (0.46–0.71)[a]	0.70 (0.50–0.97)[a]
Coronary artery disease	1.26 (1.08–1.46)[a]	1.83 (1.52–2.21)[a]	1.39 (1.03–1.89)[a]
Prior ischemic stroke	1.21 (1.02–1.43)[a]	1.54 (1.24–1.91)[b]	1.50 (1.07–2.09)[b]
Prior antithrombotic treatment[c]	1.46 (1.30–1.64)[a]	1.99 (1.69–2.34)[a]	1.63 (1.26–2.09)[a]
Low GFR	2.14 (1.88–2.45)[a]	2.97 (2.52–3.51)[a]	1.86 (1.43–2.42)[a]
High GFR	0.54 (0.31–0.97)[a]	0.44 (0.14–1.43)	0.36 (0.05–2.64)
Decreasing GFR (by 10 mL/min/1.73 m^2)	1.20 (1.17–1.24)[a]	1.33 (1.28–1.38)[a]	1.16 (1.02–1.22)[a]
Very low GFR[b]	2.66 (1.83–3.87)[a]	3.76 (2.61–5.41)[a]	1.19 (0.58–2.47)

Abbreviations: ECASS = European Cooperative Acute Stroke Study; GFR = glomerular filtration rate; IVT = IV thrombolysis; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; sICH = symptomatic intracranial hemorrhage.
Data are odds ratio (95% confidence interval). Very low GFR <30 mL/min/1.73 m^2; low GFR <60 mL/min/1.73 m^2; high GFR >120 mL/min/1.73 m^2.
[a] Statistically significant ($p < 0.05$).
[b] $p < 0.1$ (i.e., adjusted for in the multivariate analysis).
[c] Post hoc analyses, very low GFR n = 129, poor outcome = 88, death = 49, $sICH_{ECASS-II}$ = 8.

Table 3 Multivariate analysis of primary outcomes (odds adjusted for all variables with $p < 0.1$ in the univariate analysis) in patients treated with IVT

Predictors for	Poor outcome	Death	$sICH_{ECASS-II}$
Age (each year)	1.05 (1.04–1.05), <0.001	1.05 (1.04–1.07), <0.001	NS
Sex	1.21 (1.04–1.41), 0.014	NS	NS
NIHSS (each point)	1.19 (1.17–1.21), <0.001	1.15 (1.13–1.17), <0.001	1.05 (1.03–1.07), <0.001
Glucose (each mg/dL)	1.09 (1.05–1.12), <0.001	1.09 (1.05–1.14), <0.001	NS
Diabetes mellitus	1.25 (1.001–1.55), 0.049	NS	NS
Hypercholesterolemia	0.83 (0.71–0.98), 0.025	NS	NS
Current smoking	1.49 (1.23–1.80), <0.001	NS	NS
Prior stroke	NS	1.33 (1.004–1.77), 0.047	NS
Low GFR	1.32 (1.10–1.58), 0.003	1.73 (1.39–2.14), <0.001	1.64 (1.21–2.23), 0.001
High GFR[a]	1.38 (0.69–2.79), 0.364	NS	NS
Decreasing GFR (by 10 mL/min/1.73 m^2)	1.05 (1.01–1.09), 0.017	1.18 (1.11–1.24), <0.001	1.11 (1.04–1.20), 0.003
Post hoc analyses			
Very low GFR[a]	1.96 (1.27–3.04), 0.003	2.53 (1.65–3.87), <0.001	NS

Abbreviations: ECASS = European Cooperative Acute Stroke Study; GFR = glomerular filtration rate; IVT = IV thrombolysis; NIHSS = NIH Stroke Scale; NS = not significant ($p > 0.05$); sICH = symptomatic intracranial hemorrhage.
Data are odds ratio (95% confidence interval), p value. Very low GFR <30 mL/min/1.73 m^2; low GFR <60 mL/min/1.73 m^2; high GFR >120 mL/min/1.73 m^2.
[a] Adjusted only for age and NIHSS score because of the small sample size.

Fourth, the choice of criteria for the primary outcome measures might be considered arbitrary. Interestingly, there were virtually no differences in the odds between the primary (mRS scores 3–6) and the secondary functional outcome measures (mRS scores 2–6) as well as for sICH according to the ECASS-II and NINDS criteria. This might be an argument for the robustness of our findings and the prognostic importance of renal function in IVT-treated patients.

AUTHOR CONTRIBUTIONS

H.G. designed/conceptualized the study, analyzed/interpreted the data, drafted the manuscript, and collected data. S.M.Z. revised the manuscript, and collected data. Y.B.R. analyzed/interpreted the data, revised the manuscript, and collected data. D.J.S., P.R., V.A., J.P., E.H., D.L., R.B., P.M., C.O., J.B., M.A., M.R.H., A.Z., G.B., V.P., N.P., and A.P. revised the manuscript, and collected data. C.S. performed advanced statistical analyses on the shape of the relation between the probability of the primary outcome measures and GFR, described them and interpreted their results. H.S. and L.H.B. revised the manuscript, and collected data. T.T. designed/conceptualized the study, revised the manuscript, and collected data. P.A.L. revised the manuscript, and collected data. P.J.N. designed/conceptualized and initiated the study, analyzed/interpreted the data, revised the manuscript, and collected data. S.T.E. designed/conceptualized and initiated the study, supervised the study, analyzed/interpreted the data, revised the manuscript, and collected data.

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Lundbeck A/S, Sanofi-Aventis, Concentric Medical, and Mitsubishi Pharma; he is editor-in-chief of *Case Reports in Neurology*, serves on the editorial boards of *Stroke*, *Cerebrovascular Diseases*, *Current Vascular Pharmacology*, *The Open Pharmacology Journal*, *Clinics of Turkey*, *Clinics of Turkey/Neurology*, *The Open Cardiovascular Medicine Journal*, *Recent Patents on Biotechmology*, *Recent Patents on CND Drug Discovery*, *Experimental and Translational Stroke Medicine*, *Stroke Research and Treatment*, *BMC Journal of Experimental and Translational Stroke Medicine*, and *Frontiers in Stroke*; has filed patents: stanniocalcin proteins and nucleic acids and methods based thereon, new therapeutic uses (method to prevent brain edema and reperfusion injury), and thrombolytic compositions (method to prevent postthrombolytic hemorrhage formation); he receives/has received research support from Boehringer Ingelheim (payment for development of education material), the Finnish Academy of Sciences, the Finnish Medical Foundation, the European Union, Biocenter Finland, Biocentrum Helsinki, the Helsinki University Central Hospital, Sigrid Juselius Foundation, Liv och Hälsa, Maire Taponen Foundation, and the NIH; has received research or teaching awards from the Finnish Medical Association in 2010 (quality award in health care with telestroke innovation), SalusAnsvar Foundation in Sweden in 2011 (excellence in stroke medicine), Finnish Young Physicians in 2005 (best mentor in medical education in Finland in 2004), and the University of Helsinki in 2004 and 2009 (supervisor of best MD thesis in medicine in 2003 and 2008); he has received speakers bureau compensation from Professio Finland, the University of Helsinki, the Finnish Medical Association, University of Donau (Austria), Genzyme Oy, and the Finnish Neurological Association. 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