Original Article

Chronic Kidney Disease and Bleeding Complications After Intravenous Thrombolytic Therapy for Acute Ischemic Stroke

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Background—The safety of intravenous thrombolysis in ischemic stroke (IS) patients with chronic kidney disease (CKD) is uncertain. We assessed whether CKD is associated with bleeding complications after intravenous tissue-type plasminogen activator administration to patients with IS.

Methods and Results—Data were analyzed from 44 410 patients with IS treated with intravenous tissue-type plasminogen activator in the Get With The Guidelines-Stroke Program. Glomerular filtration rate based on admission serum creatinine was categorized as dichotomous (presence of CKD as <60) or as distinct categories: normal (≥90), mild (≥60–<90), moderate (≥30–< 60), severe (≥15–<30), and kidney failure (<15 or dialysis). Primary outcomes evaluated were symptomatic intracranial hemorrhage and serious systemic hemorrhage; secondary outcomes were in-hospital mortality, independent functional status. There were 15 191 of 44 410 (34%) intravenous tissue-type plasminogen activator-treated IS patients with CKD. Presence of CKD (versus no CKD) was not associated with risk-adjusted symptomatic intracranial hemorrhage (adjusted odds ratio, 1.0; 95% confidence interval: 0.91–1.10) or serious systemic hemorrhage (adjusted odds ratio, 0.97; 95% confidence interval: 0.80–1.18) and did not significantly vary by kidney dysfunction stage for either of these primary end points in multivariable analyses. Compared with patients with normal kidney function, those with CKD were more likely to die in the hospital (adjusted odds ratio, 1.22; 95% confidence interval: 1.14–1.32) and have an unfavorable discharge functional status (adjusted odds ratio, 1.13; 95% CI: 1.07–1.19).

Conclusions—Presence of CKD among patients with IS treated with intravenous tissue-type plasminogen activator is associated with higher unadjusted odds of symptomatic intracranial hemorrhage or serious systemic hemorrhage, but this is explained by non-CKD related factors. (***Circ Cardiovasc Qual Outcomes***. 2014;7:929-935.)

Key Words: glomerular filtration rate ■ hemorrhage ■ prognosis ■ renal Insufficiency, chronic

Chronic kidney disease (CKD) is highly prevalent among hospitalized patients with stroke and is an independent predictor of poor clinical outcomes in these patients.[1] Although intravenous tissue-type plasminogen activator (IV tPA) can reverse the damaging consequences of acute ischemic stroke (AIS),[2,3] its administration to AIS patients with CKD is viewed with some caution because (1) presence of CKD was not specifically distinguished in the pivotal IV tPA clinical trials; and (2) patients with CKD tend to have a higher prevalence of hemorrhagic transformation, cerebral microbleeds, and systemic hemorrhages,[4] and IV tPA is associated with an increased risk of symptomatic intracranial hemorrhage (sICH).[2,3]

Published studies that have explored outcomes among AIS patients with CKD treated with IV tPA have shown conflicting results.[5–10] These studies have generally been of modest sample size, based on patients from a single center, or evaluated only biomarker outcomes.[5–11] Furthermore, none of these studies examined the association of the various clinical categories of CKD severity with thrombolytic outcomes among patients with AIS or assessed an end point of systemic hemorrhage.

To address the need for analysis of a large, practice-based data set, that permits the evaluation of clinically important bleeding complications by established CKD staging, the US national Get With The Guidelines-Stroke (GWTG-Stroke)

WHAT IS KNOWN

- Chronic kidney disease (CKD) is highly prevalent among hospitalized patients with stroke. Influence of CKD on outcome was not specifically distinguished in the pivotal intravenous tissue-type plasminogen activator clinical trials.
- In general, patients with CKD tend to have a higher prevalence of cerebral microbleeds and systemic hemorrhages.

WHAT THE STUDY ADDS

- Largest study to date to examine symptomatic intracranial hemorrhage and other bleeding risk among intravenous tissue-type plasminogen activator–treated patients with ischemic stroke in terms of presence and severity of CKD.
- Findings imply that presence of CKD alone should not be a contraindication to administration of intravenous tissue-type plasminogen activator to eligible patients with ischemic stroke from a hemorrhagic risk standpoint.

registry was analyzed to determine the association of CKD with key hemorrhagic outcomes after IV tPA for AIS.

Methods

GWTG-Stroke is a national registry implemented by the American Heart Association and American Stroke Association to support continuous quality improvement of hospital systems of care for patients with stroke and transient ischemic attack. Details of the design and conduct of the program have been previously described.[12] GWTG uses a web-based patient management tool (Outcome, Quintiles Company) to collect clinical data on consecutively admitted patients, to provide decision support, and to enable real-time online reporting features. After an initial pilot phase, the GWTG-Stroke Program was made available in April 2003 to any hospital in the United States. GWTG-Stroke participating hospitals record data from consecutive stroke and transient ischemic attack hospital admissions. Case ascertainment is done via clinical identification during the hospital encounter, retrospective surveillance of *International Classification of Diseases, 9th Revision* codes, or both. Trained hospital personnel extract data on demographics, medical history, neuroimaging, in-hospital treatment, and discharge characteristics. Although the GWTG-Stroke program is overrepresented with larger academic teaching hospitals, the patient demographics and comorbidites are similar to those described in other stroke registries and administrative databases.[12] Outcome Sciences serves as the data collection and coordination center for GWTG. The Duke Clinical Research Institute serves as the data analysis center and has an agreement to analyze the aggregate deidentified data for research purposes. Each participating hospital received either human research approval to enroll cases without individual patient consent under the common rule or a waiver of authorization and exemption from subsequent review by their institutional review board.

The serum creatinine level obtained at the time of hospital admission was used to determine the estimated glomerular filtration rate (GFR). Estimated GFR per the Modification of Diet in Renal Disease Study Group equation was calculated for each patient using the abbreviated Modification of Diet in Renal Disease formula: estimated GFR (mL/min per 1.73 m²)=186×(serum creatinine)−1.154×age−0.203×(0.742 if female)×(1.21 if black).[13] CKD was defined as estimated GFR <60 mL/min per 1.73 m² . GWTG-Stroke patients

without CKD (controls) were the referent group for purposes of comparison. We then categorized patients by kidney function (GFR in mL/min per 1.73 m²) using modified definitions from the National Kidney Foundation—Kidney Disease Outcomes Quality Initiative clinical practice guidelines: normal (GFR ≥90), mild (60≤ GFR <90), moderate (30≤ GFR <60), severe (15≤ GFR <30), and kidney failure (GFR <15).[13] These distinct categories of kidney dysfunction were analyzed with GFR ≥90 as the referent category. The primary outcomes were post-IV tPA sICH and serious systemic hemorrhage (SSH) within 36 hours. Post-IV tPA sICH was defined as neurological worsening within 36 hours of tPA administration that is attributed to ICH verified by computed tomography or MRI, as documented in the chart by the treating physician. This definition is based on the criteria for sICH in the 1995 National Institute of Neurological Disorders and Stroke (NINDS) trial.[2] Secondary study end points included in-hospital mortality and lack of independent functional status at discharge. In-hospital deaths are captured by the detailed review of the medical records and entered into the electronic case report form. Functional status is captured by documented ambulatory status at time of discharge in the following categories (1) able to ambulate independently (no help from another person) with or without a device (such as cane), (2) with assistance (from person), (3) unable to ambulate, and (4) not documented.

Statistical Analysis

Pearson χ^2 test was used to compare the categorical variables between patients with and without CKD and to compare variables among CKD stages; and Kruskal–Wallis test was used for continuous variables. The relationship between CKD status (yes versus no) and different levels of renal function versus outcomes was further examined using multivariable logistic regression models. To account for within-hospital clustering, generalized estimating equations were used to generate unadjusted and adjusted models.[14] Confidence intervals (CIs) and P values were computed using Wald tests. The adjusted models included the following prespecified potential confounders: age, sex, race, medical history (including atrial fibrillation, prosthetic heart valve, previous stroke/transient ischemic attack, coronary heart disease/previous myocardial infarction, carotid stenosis, peripheral vascular disease, hypertension, diabetes mellitus, dyslipidemia, heart failure, and current smoking), prior medication use (premorbid antiplatelet or anticoagulant drugs), systolic blood pressure at admission, hospital size, region, teaching status, primary stroke center status, and the number of annual stroke discharges from each hospital. Missing values for medical history (0.22%) were imputed to no history and for systolic blood pressure (2.62%) to the median value. Patients with missing information in one or more hospitals characteristics were excluded from the models (<0.25%).

We also conducted sensitivity analyses by generating models that included all of the aforementioned variables and the measure of stroke severity (National Institutes of Health Stroke Scale Score [NIHSS]) in the subgroup of patients in which this measure of stroke severity was documented (NIHSS missing in 8.1% of study population with those cases excluded from analysis). NIHSS was analyzed as a continuous variable. Finally, we evaluated mortality rates by each tPA complication variable (ICH, SSH, any, other), first overall and then by each CKD severity group. All tests are 2-tailed with P<0.05 considered as the level of statistical significance. All statistical analyses were performed using SAS software (version 9.2, SAS Institute Inc, Cary, NC).

Results

Of 858 124 AIS admissions at 1624 hospitals during the study period, after excluding patients ineligible for study inclusion, there were 44 410 eligible IV tPA-treated patients at 1326 hospitals with complete data (Figure I in the Data Supplement). Among these patients, about a third (34.2%; n=15 191) met the definition of CKD. Patients with CKD were older (mean, 76.5 versus 66.7 years), more likely to

be female, or white, and more likely to have a medical history of stroke/transient ischemic attack, carotid stenosis, coronary artery disease/previous myocardial infarction, hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation/flutter, peripheral arterial disease, and heart failure, but they were less likely to be current smokers. Patients with CKD had more severe strokes (mean NIH stroke scale score 13.0 versus 11.3). Table 1 compares the demographic and clinical characteristics of IV tPA-treated patients with ischemic stroke by presence and stage of CKD. Compared with patients with earlier stages of kidney dysfunction (mild or moderate), those with more advanced stages of dysfunction (severe CKD or renal failure) were more likely to be of black race and have a medical history of diabetes mellitus, peripheral arterial disease, and heart failure but less likely to be on medications for diabetes mellitus, be able to ambulate independently prior to admission, and have strokes of mild severity.

Table 1. Baseline Patient Characteristics of IV tPA-Treated Patients by Chronic Kidney Disease Stage

Variable	Normal Function (GFR≥90) (N=9788)		Mild CKD (GFR ≥60 to <90) (N=19431)		Moderate CKD (GFR ≥30 to <60) (N=13097)		Severe CKD (GFR ≥15 to <30) (N=1516)		Renal Failure (GFR<15) (N=578)		P Value*
Demographics											
Mean age, y SD	60.60	14.96	69.76	14.34	76.78	11.77	77.39	12.61	68.37	14.11	<0.0001
Female sex, n (%)	4092	41.81	9176	47.22	7984	60.96	976	64.38	323	55.88	<0.0001
White race, n (%)	6147	62.80	14288	73.53	10166	77.62	1105	72.89	322	55.71	<0.0001
Black race, n (%)	2143	21.89	2639	13.58	1386	10.58	220	14.51	154	26.64	
Hispanic ethnicity, n (%)	907	9.27	1266	6.52	795	6.07	103	6.79	64	11.07	
Arrival information											
EMS arrival from home/scene, n (%)	7423	75.84	15576	80.16	11068	84.51	1308	86.28	468	80.97	<0.0001
Median LKW to arrival in minutes; 25th, 75th percentile	61	40, 97	59	39, 90	58	38, 86	60	40, 90	57	38, 91	<0.0001
Past medical history, n (%)											
Atrial fib/flutter	1134	11.62	3999	20.62	3669	28.09	442	29.19	134	23.22	<0.0001
CAD/prior MI	1794	18.38	4597	23.70	4220	32.31	584	38.57	191	33.10	<0.0001
Carotid stenosis	152	1.56	502	2.59	478	3.66	64	4.23	9	1.56	<0.0001
Diabetes mellitus	2291	23.47	4345	22.40	3859	29.54	672	44.39	296	51.30	<0.0001
Dyslipidemia	3211	32.90	7802	40.23	6001	45.94	692	45.71	225	38.99	<0.0001
Hypertension	6042	61.90	13857	71.45	10797	82.66	1318	87.05	491	85.10	<0.0001
Prosthetic heart valve	99	1.01	210	1.08	171	1.31	23	1.52	3	0.52	0.0579
Peripheral vascular Dx	192	1.97	570	2.94	578	4.43	119	7.86	45	7.80	<0.0001
Heart failure	444	4.55	1417	7.31	1706	13.06	326	21.53	114	19.76	<0.0001
Active smoking	2895	29.66	3441	17.74	1462	11.19	155	10.24	73	12.65	<0.0001
Previous stroke/TIA	2084	21.35	4647	23.96	3605	27.60	451	29.79	164	28.42	<0.0001
Independent ambulation	8570	87.56	16702	85.96	10811	82.55	1169	77.11	452	78.20	<0.0001
Premorbid medications, n (%)											
Anticoagulants	551	5.63	1440	7.41	1117	8.53	114	7.52	53	9.17	<0.0001
Antiplatelets	3292	33.63	8320	42.82	6741	51.47	817	53.89	273	47.23	<0.0001
Antihypertensives	5024	51.33	12649	65.10	10597	80.91	1326	87.47	468	80.97	<0.0001
Cholesterol reducers	2926	29.89	7452	38.35	6170	47.11	796	52.51	267	46.19	<0.0001
Antidiabetic drugs	1712	17.49	3337	17.17	3021	23.07	484	31.93	181	31.31	<0.0001
Admission information											
Altered consciousness, n (%)	1431	14.62	3339	17.18	2688	20.52	354	23.35	125	21.63	<0.0001
Median NIHSS; 25th, 75th percentile	9	5, 15	10	6, 17	12	7, 18	12	7, 19	11	6, 17	<0.0001
Door to computed tomography ≤25 min, n (%)	5749	58.74	11986	61.68	8094	61.80	921	60.75	322	55.71	<0.0001
Mean BMI (SD), kg/m²	28.91	7.52	28.32	7.12	28.16	7.53	28.04	7.61	27.82	7.25	<0.0001
Mean systolic blood pressure (SD), mm Hg	154.73	27.75	157.46	28.01	157.70	29.79	155.49	31.27	158.42	32.13	<0.0001
Mean serum creatinine (SD), mg/dL	0.74	0.15	0.97	0.17	1.36	0.30	2.49	0.62	6.58	2.72	<0.0001

BMI indicates body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; EMS, Emergency Medical Services; GFR, glomerular filtration rate; IV tPA, intravenous tissue-type plasminogen activator; LKW, last known well; MI, myocardial infarction; NIHSS, National Institutes of Health Stroke Scale Score; and TIA, transient ischemic attack.

*Comparisons of differences across the 5 CKD groups.

Table 2.   Unadjusted Frequencies Comparing Intravenous Thrombolysis Outcomes Among Patients With Ischemic Stroke by Presence of Chronic Kidney Disease

	Overall (N=44 410)		No CKD (GFR≥90) (N=29 219)		CKD (GFR<60) (N=15 191)		
Outcome	n	%	n	%	n	%	P Value
Symptomatic intracranial hemorrhage	2053	4.62	1229	4.21	824	5.42	<0.0001
Serious systemic hemorrhage	441	0.99	260	0.89	181	1.19	0.0023
In-hospital mortality	3528	7.94	1898	6.50	1630	10.73	<0.0001
No independent ambulation at discharge	20 034	49.00	12 318	45.09	7716	56.90	<0.0001

CKD indicates chronic kidney disease; and GFR, glomerular filtration rate.

As shown in Table 2, patients with CKD (versus no CKD) were significantly more likely to experience sICH (5.4 versus 4.2%), SSH (1.2 versus 0.9%), in-hospital mortality (10.7 versus 6.5%), and lack of independent functional status (56.9 versus 45.1%). Results of analysis by renal dysfunction stage revealed no clear trend in the frequency of sICH or SSH across CKD stages, but there was a pattern of higher frequency of inpatient mortality and lack of independent functional status with progressively more severe renal dysfunction (Table 3).

Table 4 shows unadjusted and adjusted odds ratios (ORs) comparing IV tPA-treated patients with ischemic stroke by presence of CKD and across various stages of renal dysfunction to those with normal function for the various outcome measures. These results are adjusted for patient characteristics only because further adjustment for hospital characteristics made little difference. Presence of CKD (versus no CKD) was not associated with sICH (adjusted OR, 1.00; 95% CI: 0.91–1.10) or SSH (adjusted OR, 0.97; 95% CI: 0.80–1.18) and did not significantly vary by renal dysfunction stage for either of these primary end points in multivariable analyses (Table 4). However, in-hospital case fatality was higher for patients with CKD versus no CKD (adjusted OR, 1.22; 95% CI: 1.14–1.32) and progressively rose with more severe renal dysfunction. A similar pattern of poorer outcomes with more severe renal impairment was seen with lack of independent functional status at discharge.

Table 5 shows the comparison of IV tPA-treated patients with ischemic stroke by presence of CKD and various stages

of renal dysfunction to those with normal function, additionally controlling for the measure of stroke severity (NIHSS). Similar to the analyses without inclusion of NIHSS, these results are adjusted for patient characteristics only because further adjustment for hospital characteristics made little difference. Presence of CKD (versus no CKD) was not associated with sICH (adjusted OR, 0.99; 95% CI: 0.89–1.09) or SSH (adjusted OR, 0.97; 95% CI: 0.79–1.19) and did not significantly vary by kidney dysfunction stage for either of these primary end points in multivariable analyses (Table 5). However, in-hospital case fatality was higher for IV tPA-treated ischemic stroke patients with CKD versus no CKD (adjusted OR, 1.19; 95% CI: 1.09–1.30) and progressively rose with more severe renal dysfunction. A similar pattern of poorer outcomes with more severe renal impairment was seen with lack of independent functional status at discharge. Table I in the Data Supplement shows in-hospital mortality rates by each complication variable, overall patient population and by each CKD severity stage. There were much higher in-hospital mortality rates in tPA-treated ischemic stroke patients with sICH and SSH than those without either of these bleeding outcomes, both overall and within each CKD severity category. Table II in the Data Supplement shows the adjusted ORs for all patient demographic covariates associated with sICH as an outcome.

Discussion

As far as are aware, to date this is the largest description and analysis of sICH and other bleeding risk among tPA-treated patients with ischemic stroke in terms of presence and severity of CKD. We found that although the risks of sICH or SSH were modestly higher in unadjusted analyses, we did not observe any independent relationships between presence of CKD and occurrence of either sICH or SSH in these patients. The lack of relationship of renal dysfunction with sICH is consistent with a prior analysis of sICH predictors within the GWTG-Stroke data set that found no relationship of serum creatinine with sICH.[15] Perhaps not surprisingly, among IV tPA-treated patients with ischemic stroke, the odds of dying in the hospital after adjusting for major confounders was 23% higher for those patients with CKD compared with those without CKD, and the independent association of kidney impairment with in-hospital mortality increased progressively with worsening renal dysfunction. Placing our overall findings in their full context suggests that the poor clinical outcomes linked to CKD in IV tPA-treated patients with

Table 3.   Unadjusted Frequencies Comparing Intravenous Thrombolysis Outcomes Among Patients With Ischemic Stroke With Various Stages of Renal Dysfunction to Those With Normal Renal Function

	Overall (N=44 410)		Normal Function (GFR≥90) (N=9788)		Mild CKD (GFR ≥60 to <90) (N=19 431)		Moderate CKD (GFR ≥30 to <60) (N=13 097)		Severe CKD (GFR ≥15 to <30) (N=1516)		Renal Failure (GFR<15) (N=578)		
Outcome	n	%	n	%	n	%	n	%	n	%	n	%	P Value
Symptomatic intracranial hemorrhage	2053	4.62	327	3.34	902	4.64	729	5.57	78	5.15	17	2.94	<0.0001
Serious systemic hemorrhage	441	0.99	67	0.68	193	0.99	158	1.21	17	1.12	6	1.04	0.0032
In-hospital mortality	3528	7.94	482	4.92	1416	7.29	1341	10.24	211	13.92	78	13.49	<0.0001
No independent Ambulation at discharge	20 034	49.00	3862	41.50	8456	46.94	6629	56.39	814	62.38	273	54.60	

CKD indicates chronic kidney disease; and GFR, glomerular filtration rate.

Table 4. Unadjusted and Adjusted Odds Ratios Comparing IV tPA-Treated Patients With Ischemic Stroke With Various Stages of Kidney Dysfunction to Those Without CKD for the Outcome Measures (NIHSS Score Not in the Model)

Outcome	CKD Categorization	Description	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Symptomatic intracranial hemorrhage	Dichotomous	CKD (GFR<60)	1.30 (1.18–1.42)*	<0.0001	1.00 (0.91–1.10)*	0.9510
	Polytomous	Mild dysfunction (GFR ≥60 to <90)	1.40 (1.23–1.58)†	<0.0001	1.08 (0.95–1.23)†	0.2394
		Moderate dysfunction (GFR ≥30 to <60)	1.69 (1.48–1.92)†	<0.0001	1.09 (0.95–1.26)†	0.2233
		Severe dysfunction (GFR ≥15 to <30)	1.57 (1.22–2.00)†	0.0004	0.99 (0.76–1.27)†	0.9079
		Renal failure (GFR<15)	0.87 (0.53–1.42)†	0.5762	0.65 (0.39–1.06)†	0.0852
Severe systemic hemorrhage	Dichotomous	CKD (GFR<60)	1.35 (1.13–1.63)*	0.0012	0.97 (0.80–1.18)*	0.7924
	Polytomous	Mild dysfunction (GFR ≥60 to <90)	1.45 (1.09–1.93)†	0.0102	1.04 (0.78–1.39)†	0.7889
		Moderate dysfunction (GFR ≥30 to <60)	1.77 (1.35–2.34)†	<0.0001	1.01 (0.75–1.37)†	0.9398
		Severe dysfunction (GFR ≥15 to <30)	1.72 (1.04–2.87)†	0.0362	0.94 (0.55–1.60)†	0.8106
		Renal failure (GFR<15)	1.51 (0.67–3.39)†	0.3149	1.02 (0.45–2.30)†	0.9573
In-hospital mortality	Dichotomous	CKD (GFR<60)	1.74 (1.61–1.87)*	<0.0001	1.22 (1.14–1.32)*	<0.0001
	Polytomous	Mild CKD (GFR ≥60 to <90)	1.52 (1.37–1.70)†	<0.0001	1.09 (0.97–1.22)†	0.1332
		Moderate CKD (GFR ≥30 to <60)	2.23 (2.00–2.49)†	<0.0001	1.24 (1.10–1.40)†	0.0004
		Severe CKD (GFR ≥15 to <30)	3.16 (2.66–3.77)†	<0.0001	1.64 (1.37–1.97)†	<0.0001
		Renal failure (GFR<15)	3.01 (2.33–3.89)†	<0.0001	2.07 (1.59–2.69)†	<0.0001
Lack of independent ambulation at discharge	Dichotomous	CKD (GFR<60)	1.80 (1.72–1.89)*	<0.0001	1.13 (1.07–1.19)*	<0.0001
	Polytomous	Mild CKD (GFR ≥60 to <90)	1.30 (1.24–1.38)†	<0.0001	0.88 (0.82–0.93)†	<0.0001
		Moderate CKD (GFR ≥30 to <60)	2.09 (1.97–2.23)†	<0.0001	0.99 (0.92–1.06)†	0.7553
		Severe CKD (GFR ≥15 to <30)	2.94 (2.56–3.37)†	<0.0001	1.30 (1.12–1.49)†	0.0004
		Renal failure (GFR<15)	1.89 (1.56–2.29)†	<0.0001	1.25 (1.03–1.52)†	0.0237

All models are adjusted for age, race, sex, medical history (atrial fibrillation, prosthetic heart valve, previous stroke/transient ischemic attack, coronary artery disease/previous myocardial infarction, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, heart failure, and current smoking), and prior antiplatelet or anticoagulant use. CI indicates confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; IV tPA, intravenous tissue-type plasminogen activator; NIHSS, National Institutes of Health Stroke Scale Score; and OR, odds ratio.

*Compared with glomerular filtration rate ≥60.

†Compared with glomerular filtration rate ≥90.

ischemic stroke, may be more likely because of the copresence (with CKD) of other harmful conditions like anemia, oxidative stress, electrolyte imbalances, and chronic inflammation,[16] rather than the abnormalities in coagulation and platelet function typically associated with CKD.[17] Another explanation for these results could be the greater proportion of patients encountered with CKD stages 3 to 4 versus stage 5. CKD stages 3 to 4 are linked with a higher frequency of atherosclerosis and thrombotic vascular complications (ie, high atherosclerotic vascular burden leading to worse outcomes) than the other CKD stages while platelet dysfunction (higher risk of bleeding) has largely been described only in patients with uremia such as in CKD stage 5.[16,17]

Data from previously published studies that have examined this issue were based on patient populations numbering less than a 1000 and revealed differing results.[5–11] A retrospective study of 578 Japanese patients showed that among patients with ischemic stroke treated with IV tPA renal dysfunction was associated with early intracranial bleeding and poor outcomes,[5] a study of 740 patients in Germany revealed that only severe renal impairment was associated with sICH after IV tPA treatment,[6] another study (n=196) found that patients with ischemic stroke treated with IV tPA who had impaired renal function tended (P=0.096) to have more sICH,[7] and finally a single center retrospective analysis of 224 patients showed increased odds of sICH with kidney impairment but serum creatinine, not GFR was the index of renal function.[8] However, 2 other studies indicated that IV tPA treatment in ischemic stroke patients with CKD was not associated with increased risk of ICH, poor functional outcome, or in-hospital death.[9,10] A sixth study (n=229) found that patients with ischemic stroke treated with IV tPA who had renal dysfunction

Table 5.   Unadjusted and Adjusted Odds Ratios Comparing IV tPA-Treated Patients With Ischemic Stroke With Various Categories of CKD to Those Without CKD for the Outcome Measures (NIHSS Score in the Model)

Outcome	CKD Categorization	Category of CKD	Unadjusted OR (95% CI)	P Value	Adjusted OR (95% CI)	P Value
Symptomatic intracranial hemorrhage	Dichotomous	CKD (GFR<60)	1.30 (1.18–1.43)*	<0.0001	0.99 (0.89–1.09)*	0.7767
	Polytomous	Mild dysfunction (GFR ≥60 to <90)	1.39 (1.22–1.58)†	<0.0001	1.08 (0.94–1.24)†	0.2525
		Moderate dysfunction (GFR ≥30 to <60)	1.69 (1.48–1.94)†	<0.0001	1.08 (0.93–1.26)†	0.2941
		Severe dysfunction (GFR ≥15 to <30)	1.50 (1.15–1.95)†	0.0028	0.92 (0.70–1.21)†	0.5385
		Renal failure (GFR<15)	0.83 (0.49–1.39)†	0.4774	0.60 (0.35–1.03)†	0.0628
Severe systemic hemorrhage	Dichotomous	CKD (GFR<60)	1.40 (1.15–1.70)*	0.0006	0.97 (0.79–1.19)*	0.7819
	Polytomous	Mild dysfunction (GFR ≥60 to <90)	1.69 (1.26–2.26)†	0.0005	1.22 (0.90–1.65)†	0.1914
		Moderate dysfunction (GFR ≥30 to <60)	2.05 (1.53–2.73)†	<0.0001	1.14 (0.84–1.56)†	0.3999
		Severe dysfunction (GFR ≥15 to <30)	2.03 (1.20–3.42)†	0.0082	1.05 (0.61–1.83)†	0.8519
		Renal failure (GFR<15)	1.87 (0.82–4.28)†	0.1358	1.25 (0.54–2.88)†	0.5964
In-hospital mortality	Dichotomous	Any CKD (GFR<60)	1.74 (1.61–1.88)*	<0.0001	1.19 (1.09–1.30)†	0.0001
	Polytomous	Mild CKD (GFR ≥60 to <90)	1.53 (1.36–1.71)†	<0.0001	1.10 (0.97–1.24)†	0.1301
		Moderate CKD (GFR ≥30 to <60)	2.22 (1.97–2.50)†	<0.0001	1.20 (1.05–1.38)†	0.0064
		Severe CKD (GFR ≥15 to <30)	3.20 (2.66–3.85)†	<0.0001	1.66 (1.35–2.04)†	<0.0001
		Renal failure (GFR<15)	3.10 (2.38–4.06)†	<0.0001	2.21 (1.65–2.96)†	<0.0001
Lack of independent ambulation at discharge	Dichotomous	Any CKD (GFR<60)	1.82 (1.73–1.91)*	<0.0001	1.13 (1.07–1.19)*	<0.0001
	Polytomous	Mild CKD (GFR ≥60 to <90)	1.31 (1.24–1.39)†	<0.0001	0.88 (0.82–0.94)†	0.0002
		Moderate CKD (GFR ≥30 to <60)	2.13 (1.99–2.27)†	<0.0001	1.00 (0.92–1.08)†	0.9047
		Severe CKD (GFR ≥15 to <30)	2.96 (2.56–3.41)†	<0.0001	1.29 (1.10–1.52)†	0.0019
		Renal failure (GFR<15)	1.81 (1.48–2.20)†	<0.0001	1.21 (0.98–1.49)†	0.0697

All models are adjusted for age, race, sex, medical history (atrial fibrillation, prosthetic heart valve, previous stroke/ transient ischemic attack, coronary artery disease/previous myocardial infarction, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, heart failure, and current smoking), prior antiplatelet or anticoagulant use, and National Institutes of Health Stroke Scale score. Analyses confined to 91.2% of patients with NIHSS documented. CI indicates confidence interval; CKD, chronic kidney disease; GFR, glomerular filtration rate; IV tPA, intravenous tissue-type plasminogen activator; NIHSS, National Institutes of Health Stroke Scale Score; and OR, odds ratio.

*Compared with glomerular filtration rate ≥60.

†Compared with glomerular filtration rate ≥90.

(versus normal function) experienced reduced improvement in NIHSS score at 24 hours but had similar rates of ICH.[11] Our study with >44 000 ischemic stroke cases treated at 1326 hospitals, by far the largest to date on this issue, with its ability to also examine the relationships of specific stages of CKD to several end points including a major complication of IV tPA treatment (sICH),[2,3] an incontrovertible outcome (mortality), and an outcome primarily used in several defining trials of IV tPA (independent functional status),[2,3] may make it possibly the most definitive report thus far.

Nonetheless, this study has limitations. First, data were obtained from the medical record and depended on the accuracy and completeness of clinical. Second, although we controlled for known confounders, unmeasured confounding could have affected our results. For instance, it is possible that clinicians may have selected patients with CKD at presumably lower risk for hemorrhagic complications. Third, we only examined in-hospital outcomes, therefore, the long-term impact of CKD in this study on stroke-related outcomes was not determined. Fourth, although the Modification of Diet in Renal Disease formula is the preferred method for estimating renal function, it should ideally be used when renal function is stable, and this may not be the case for many patients admitted with AIS. However, our intent was not to determine precise renal function but to estimate the degree of renal impairment in a large cohort of patients hospitalized with AIS. Fifth, information on whether patients were on peritoneal or hemodialysis was not collected, especially because it would have been helpful to know how proximity in time of hemodialysis to stroke onset may have influenced our results. Data

on renal transplantation were also not collected. Finally, there is the possibility that the higher in-hospital death rate among advanced patients with CKD was because of severe hemorrhage that was not coded as bleeding in the GWTG data. With rigorous checks against source documentation, the fact that our overall sICH rates with tPA are similar to other reports, and the much higher in-hospital mortality rates in tPA-treated patients with sICH and SSH versus those without (indirectly implying that relatively few sICH and SSH cases resulting in death were being missed), we think the likelihood of missing clinically significant bleeding cases was low.

In conclusion, in this large contemporary multisite study we observed that patients with CKD had a higher risk of sICH and SSH but that the presence of renal impairment was not independently linked to these major complications of IV tPA use. Furthermore, this study confirmed that renal dysfunction was progressively and independently associated with significantly higher odds of inpatient mortality among hospitalized patients with ischemic stroke treated with IV tPA. These results suggest that poor outcomes attributable to CKD may be because of other adverse conditions linked to CKD, and so presence of CKD alone should not necessarily be a contraindication to administration of IV tPA to eligible patients with ischemic stroke, particularly from a hemorrhagic risk standpoint.

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Disclosures

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