ORIGINAL RESEARCH

Patterns of Care Quality and Prognosis Among Hospitalized Ischemic Stroke Patients With Chronic Kidney Disease

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***Background*—**Relatively little is known about the quality of care and outcomes for hospitalized ischemic stroke patients with chronic kidney disease (CKD). We examined quality of care and in-hospital prognoses among patients with CKD in the Get With The Guidelines–Stroke (GWTG-Stroke) program

***Methods and Results*—**We analyzed 679 827 patients hospitalized with ischemic stroke from 1564 US centers participating in the GWTG-Stroke program between January 2009 and December 2012. Use of 7 predefined ischemic stroke performance measures, composite "defect-free" care compliance, and in-hospital mortality were examined based on glomerular filtration rate (GFR) categorized as a dichotomous (+CKD as <60) or rank-ordered variable: normal (≥90), mild (≥60 to <90), moderate (≥30 to <60), severe (≥15 to <30), and kidney failure (<15 or dialysis). There were 236 662 (35%) ischemic stroke patients with CKD. Patients with severe renal dysfunction or failure were significantly less likely to receive guideline-based therapies. Compared with patients with normal kidney function (≥90), those with CKD (adjusted OR 0.91 [95% CI: 0.89 to 0.92]), moderate dysfunction (adjusted OR 0.94 [95% CI: 0.92 to 0.97]), severe dysfunction (adjusted OR 0.80 [95% CI: 0.77 to 0.84]), or failure (adjusted OR 0.72 [95% CI: 0.68 to 0.0.76]), were less likely to receive 100% defect-free care measure compliance. Inpatient mortality was higher for patients with CKD (adjusted odds ratio 1.44 [95% CI: 1.40 to 1.47]), and progressively rose with more severe renal dysfunction.

***Conclusions*—**Despite higher in-hospital mortality rates, ischemic stroke patients with CKD, especially those with greater severity of renal dysfunction, were less likely to receive important guideline-recommended therapies. **(*J Am Heart Assoc*. 2014;3: e000905 doi: 10.1161/JAHA.114.000905)**

Key Words: chronic kidney disease • glomerular Filtration Rate • guidelines • ischemic stroke • outcomes • prognosis • quality indicators • renal

Chronic kidney disease (CKD) is a frequent comorbidity among patients with symptomatic cerebrovascular disease,[1] which has been independently linked with poorer prognoses among stroke patients including greater short- and long-term risk of death.[2–6] Because most patients with CKD die of vascular causes, not progression to end-stage renal disease, more precise quantification of the co-morbid presence and effects of CKD among patients hospitalized with acute vascular events may be insightful.[1] Moreover, it is conceivable that optimal evidence-based treatment of hospitalized patients with both symptomatic vascular disease and CKD may improve clinical outcomes.[1] Recognizing this, the American Heart Association issued an expert advisory recommending that healthcare providers aggressively manage their vascular disease patients with CKD in order to sever potential causal pathways between the kidney and the heart.[7] However, little if anything is known about the quality of evidence-based care provided to hospitalized stroke patients with CKD, and whether such care may differ by level of kidney dysfunction.

The objective of this study was 3-fold: (1) properly quantify the prevalence of CKD among hospitalized ischemic stroke patients and its association with in-hospital outcomes; (2) compare the quality of stroke-related care (ie, interventions addressing the management of stroke) among ischemic stroke patients with and without CKD; (3) assess whether care quality and in-hospital outcomes vary among ischemic stroke patients by CKD stage.

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Methods

Patient Population

We used data from the Get With The Guidelines-Stroke (GWTG-Stroke) program database. Details of the design and conduct of the program have been previously described.[8] Briefly, the program is a voluntary, national, quality-improvement initiative sponsored by the American Heart Association and American Stroke Association, geared at fostering improved adherence to guideline-based care in patients hospitalized with stroke and TIA. Briefly, participating hospitals use an Internet-based Patient Management Tool (Outcome Sciences Inc, a Quintiles Company) to enter data, receive decision support, and obtain feedback through on-demand reports of performance on quality measures. GWTG-Stroke participating hospitals record data from consecutive stroke and TIA hospital admissions. Case ascertainment is done via clinical identification during the hospital encounter, retrospective surveillance of International Classification of Diseases, ninth Revision codes, or both. Trained hospital personnel extract data on demographics, medical history, neuroimaging, in-hospital treatment, and discharge characteristics. While 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.[8] 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 de-identified 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.

Performance Measures

Seven performance measures, pre-selected by the GWTG-Stroke program as primary targets for stroke quality-improvement efforts based on prevailing expert consensus treatment guidelines,[9,10] were used to compare the quality of stroke-related care between ischemic stroke admissions with and without CKD. Acute ischemic stroke performance measures were: (1) intravenous tissue plasminogen activator in patients who arrive <2 hours after symptom onset and with no contraindications to treatment; (2) antithrombotic medication (includes any aspirin, aspirin/dipyridamole, ticlopidine, clopidogrel, unfractionated heparin, low-molecular-weight heparin, and warfarin) administered within 48 hours of admission; and (3) deep vein thrombosis prophylaxis (includes heparins, heparinoids, other anticoagulants, or pneumatic compression devices) within 48 hours of admission in non-ambulatory patients. Discharge ischemic stroke performance measures were: (1) antithrombotic (includes any aspirin, aspirin/dipyridamole, ticlopidine, clopidogrel, unfractionated heparin, low-molecular-weight heparin, and warfarin) medication; (2) anticoagulation (includes therapeutic doses of warfarin, heparinoid), or other anticoagulants such as direct thrombin inhibitors) for patients with a diagnosis of atrial fibrillation or flutter (paroxysmal, persistent, or permanent); (3) cholesterol treatment (includes statins, fibrates niacin, binding resins, or selective cholesterol absorption inhibitors) if low-density lipoprotein cholesterol (LDL-C) >100 mg/dL or if LDL-C is not documented; and (4) counseling or medication for smoking cessation for patients who are current smokers (any cigarettes in past year; "smoking cessation"). The GTWG-Stroke assessment tool allows clinicians to check a box indicating a contraindication to a given performance measure and in such cases, compliance with the performance measure is seen as being met. To summarize the overall quality of stroke-related care, we calculated a defect-free measure of care, which is a binary variable calculated as the proportion of patients who received all of the interventions for which they were eligible.

CKD Definitions

The serum creatinine level obtained at the time of hospital admission was used to determine the estimated glomerular filtration rate. Estimated glomerular filtration rate 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 m^2)=186×[serum creatinine]−1.15×age−0.203×[0.742 if female]×[1.21 if black].[11] CKD was defined as eGFR<60 mL/min per 1.73 m^2. 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 m^2) 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).

Statistical Analysis

Patient demographic and clinical variables, hospital-level characteristics, and compliance with the individual and summary quality-of-care measures were compared between patients with and without CKD. Percentages and means±SD were reported for categorical and continuous variables, respectively. Pearson χ^2 test and Wilcoxon rank-sum tests

were used to compare the categorical and continuous variables, respectively, between patients with and without CKD. To compare variables among CKD stages we used Pearson χ^2 test and Kruskal Wallis tests, respectively. The relationship between CKD status (yes versus no) and different levels of renal function versus compliance with individual performance measures, as well as the defect-free summary measure of care were further examined using multivariable logistic regression models. To account for within-hospital clustering, generalized estimating equations were used to generate unadjusted and adjusted models.[12] Confidence intervals and *P* values were computed using Wald tests. The adjusted models included the following pre-specified potential confounders: age, sex, race, medical history (including atrial fibrillation, prosthetic heart valve, previous stroke/TIA, coronary heart disease, or previous myocardial infarction [coronary artery disease/previous MI], carotid stenosis, peripheral vascular disease, hypertension, diabetes, dyslipidemia, heart failure, and current smoking), systolic blood pressure (SBP) 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 SBP (2.62%) to the median value. Patients with missing information in 1 or more hospitals characteristics were excluded from the models (less than 0.25%).

Similar multivariable logistic regression analyses were performed to explore the relationship between CKD status and 2 other binary outcome measures (ie, in-hospital mortality and discharge status [home versus other]). We included the same set of pre-specified potential confounders in all 3 of these outcomes-based models, and we chose not to adjust for differences in performance measures because of the inherent problem of confounding by indication (ie, the tendency for patients with inherently poorer prognosis to receive less care). Only eligible patients for each outcome with complete data are included in each model. We also conducted sensitivity analyses by generating models that included all of the aforementioned variables and the measure of stroke severity (NIH Stroke Scale Score) in the subgroup of patients in which this measure of stroke severity was documented (NIHSS missing in 36.1% of study population). NIHSS was analyzed as a continuous variable. 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 X SAS Institute Inc).

Results

Of 858 124 ischemic stroke admissions at 1624 hospitals during the study period, after excluding patients with serum creatinine values missing (n=151 634), reported serum creatinine value out of range (ie, 0 or >20 mg/dL, n=2195), sex or race variable missing (n=979), and patient transferred out/left against medical advice/discharge status missing/ (n=23 489), there were 679 827 ischemic stroke admissions. An analysis of just those patients with serum creatinine values available versus missing revealed generally similar demographic and clinical characteristics, and where differences existed they were small and unlikely to be of major relevance (Table 1).

Among these ischemic stroke admissions (n=679 827), over one-third (34.8%; n=236 662) met the definition of CKD. Patients with CKD were older (mean, 76.2 versus 68 years), more likely to be female or white, and more likely to have a medical history of stroke/TIA, carotid stenosis, coronary artery disease/previous MI, hypertension, dyslipidemia, diabetes, 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 8.0 versus 6.7). Table 2 compares the demographic and clinical characteristics of ischemic stroke patients by presence of CKD and stage of kidney dysfunction. Compared with patients with earlier stages of kidney dysfunction (mild or moderate), those with more advanced stages of dysfunction (severe or failure) were older, more likely to be of black race, and much more likely to have a medical history of diabetes, peripheral arterial disease, and heart failure, but less likely to be of independent ambulatory status prior to admission. Patients with more advanced stages of kidney dysfunction (versus earlier stages) were more likely to present with altered level of consciousness or lower admission systolic blood pressure levels, but less likely to have strokes of mild severity.

There were significantly higher rates of compliance with all 7 performance measures and defect-free care among those without CKD compared with those with CKD. However, for some of the measures these differences were numerically rather modest. In-hospital outcomes were much worse for those with CKD versus without CKD across all 3 endpoints studied including in-hospital case fatality (Table 3). Table 4 shows a comparison of frequencies among ischemic stroke patients with various stages of kidney dysfunction. Significantly lower rates of compliance were observed with all 7 performance measures and defect-free care among those patients with more advanced stages of kidney dysfunction (versus earlier stages), but these differences were numerically very modest with the exception of patients presenting within 2 hours of ictus receiving IV tPA, for which there was a lower compliance rate ranging from 4 to 10 percentage points in those in advanced versus earlier stages of dysfunction (Table 4). In-hospital outcomes were much worse for advanced versus earlier stages of renal dysfunction including in-hospital case fatality (Table 4).

Table 1. Baseline Demographic and Clinical Characteristics by Missing Serum Creatinine Variable Status

Variable	Description	Overall (N=826 828)		Serum Creatinine Not Missing (N=679 827)		Serum Creatinine Missing (N=147 001)		*P* Value
Demographics								
Age (18 to 110), y	Mean		70.85		70.83		70.91	0.1069
	Standard deviation		14.62		14.63		14.61	
	Minimum		18.00		18.00		18.00	
	Maximum		110.00		110.00		110.00	
Sex	Female	42 8519	51.83	352 967	51.92	75 552	51.40	0.0003
Race/ethnicity	White (n, %)	584 486	70.69	480 323	70.65	104 163	70.86	<0.0001
	Black (n, %)	134 936	16.32	114 281	16.81	20 655	14.05	
	Hispanic (n, %)	53 998	6.53	44 306	6.52	9692	6.59	
Medical history								
Atrial fibrillation/flutter	Yes (n, %)	148 626	18.10	121 918	17.97	26 708	18.71	<0.0001
Coronary artery disease	Yes (n, %)	211 217	25.73	175 430	25.86	35 787	25.07	<0.0001
Carotid stenosis	Yes (n, %)	32 417	3.95	26 454	3.90	5963	4.18	<0.0001
Diabetes mellitus	Yes (n, %)	266 500	32.46	221 128	32.60	45 372	31.79	<0.0001
Dyslipidemia	Yes (n, %)	351 473	42.81	289 409	42.67	62 064	43.48	<0.0001
Hypertension	Yes (n, %)	624 904	76.11	518 145	76.39	106 759	74.80	<0.0001
Prosthetic heart valve	Yes (n, %)	10 893	1.33	8994	1.33	1899	1.33	0.8920
Peripheral vascular disease	Yes (n, %)	38 970	4.75	32 013	4.72	6957	4.87	0.0125
Heart failure	Yes (n, %)	71 959	8.76	59 341	8.75	12 618	8.84	0.2639
Smoker	Yes (n, %)	150 389	18.32	124 675	18.38	25 714	18.02	0.0012
Previous stroke/transient ischemic attack	Yes (n, %)	254 577	31.01	211 268	31.15	43 309	30.34	<0.0001
Evaluation								
National Institute of Health Stroke Scale score	0 to 9 (n, %)	385 778	46.66	316 733	46.59	69 045	46.97	<0.0001
Door to CT scan ≤25 minutes	Yes (n, %)	154 917	18.74	128 019	18.83	26 898	18.30	0.0081
Pre-admission drugs								
Anticoagulants	Yes (n, %)	84 706	10.24	75 744	11.14	8962	6.10	0.7098
Antiplatelets	Yes (n, %)	347 104	41.98	310 558	45.68	36 546	24.86	0.0216
Anti-hypertensives	Yes (n, %)	525 329	63.54	477 350	70.22	47 979	32.64	<0.0001
Cholesterol reducers	Yes (n, %)	346 488	41.91	284 590	41.86	61 898	42.11	<0.0001
Anti-diabetics	Yes (n, %)	192 618	23.30	175 644	25.84	16 974	11.55	<0.0001

CT indicates computed tomography.

Table 5 displays unadjusted and adjusted odds ratios comparing ischemic stroke patients with various stages of kidney disease to those with normal renal function for the pre-specified stroke hospitalization performance measures and the summary defect-free care measure. Compared with patients with normal kidney function, those with CKD were significantly less likely to receive smoking cessation counseling at discharge (adjusted OR 0.86, 95% CI: 0.80 to 0.93), antithrombotic prescribed within 48 hours of admission (adjusted OR 0.82, 95% CI: 0.79 to 0.85), antithrombotic at discharge (adjusted OR 0.87, 95% CI: 0.83 to 0.91), anticoagulation at discharge if there was a diagnosis of atrial fibrillation or atrial flutter (adjusted OR 0.90, 95% CI: 0.85 to 0.95), lipid modifier at discharge (adjusted OR 0.96, 95% CI: 0.93 to 0.99), and defect-free care (adjusted OR 0.91, 95% CI: 0.89 to 0.92).

Analysis by stage of kidney dysfunction (Table 5), shows that compared with patients with normal kidney function, for patients presenting within 2 hours of stroke onset who received IV tPA or for lipid modifier medication prescribed at discharge, those with severe dysfunction or renal failure versus normal kidney function were less likely to be in

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Table 2. Baseline Patient Characteristics by Chronic Kidney Disease Stage

Variable	Description	No CKD (GFR≥90) (N=163 772)		Mild CKD (60≤GFR<90) (N=279 393)		Moderate CKD (30≤GFR<60) (N=194 030)		Severe CKD (15≤GFR<30) (N=285 83)		Renal Failure (GFR<15) (N=14 049)		*P* Value
Demographics												
Age (18 to 110), y	Mean		62.21 (14.9)		71.39 (13.8)		76.81 (12.1)		75.64 (13.3)		68.10 (13.6)	
Sex	Female	70 029	42.76	13 8667	49.63	11 8221	60.93	17 898	62.62	8152	58.03	<0.0001
Ethnicity/race	White	10 1145	61.76	20 3409	72.80	14 8431	76.50	20 043	70.12	7295	51.93	<0.0001
	Black	38 863	23.73	42 165	15.09	23 851	12.29	5004	17.51	4398	31.30	
	Hispanic	13 043	7.96	16 848	6.03	11 041	5.69	1958	6.85	1416	10.08	
Arrival												
EMS arrival	EMS from home/ scene	69 622	42.51	13 7306	49.14	11 0803	57.11	17 460	61.09	7971	56.74	<0.0001
Last known well to arrival, minutes	Mean		603.01 (988)		510.11 (880.1)		469.08 (836.8)		498.07 (900.5)		570.06 (956.9)	
Past medical history												
Atrial fib/flutter	Yes	17 083	10.46	50 154	17.99	46 136	23.83	6314	22.12	2231	15.91	<0.0001
CAD/prior MI	Yes	29 045	17.78	68 260	24.49	62 387	32.22	10 698	37.48	5040	35.93	<0.0001
Carotid stenosis	Yes	4214	2.58	10 111	3.63	9911	5.12	1611	5.64	607	4.33	<0.0001
Diabetes mellitus	Yes	49 130	30.08	79 730	28.60	69 824	36.06	14 195	49.74	8249	58.81	<0.0001
Dyslipidemia	Yes	58 684	35.93	11 9513	42.87	91 530	47.27	13 576	47.57	6106	43.53	<0.0001
Hypertension	Yes	109 599	67.10	209 554	75.17	162 084	83.72	24 782	86.83	12 126	86.45	<0.0001
Prosthetic heart valve	Yes	1599	0.98	3622	1.30	3119	1.61	452	1.58	202	1.44	<0.0001
PVD	Yes	5165	3.16	11 275	4.04	11 591	5.99	2539	8.90	1443	10.29	<0.0001
Heart failure	Yes	7210	4.41	19 347	6.94	24 612	12.71	5583	19.56	2589	18.46	<0.0001
Smoker	Yes	48 775	29.86	48 747	17.49	22 166	11.45	3199	11.21	1788	12.75	<0.0001
Previous stroke/TIA	Yes	42 403	25.96	83 887	30.09	68 990	35.63	10 848	38.01	5140	36.65	<0.0001
Premorbid medications												
Anticoagulants	Yes	13 432	8.20	30 912	11.06	26 062	13.43	3695	12.93	1643	11.69	<0.0001
Antiplatelets	Yes	59 729	36.47	12 6970	45.44	101 163	52.14	15 393	53.85	7303	51.98	<0.0001
Anti-Hypertensives	Yes	91 530	55.89	190 835	68.30	158 375	81.62	24 864	86.99	11 746	83.61	<0.0001
Antilipemics	Yes	53 597	32.73	11 4952	41.14	94 150	48.52	14 793	51.75	7098	50.52	
Anti-diabetics	Yes	38 011	23.21	63 481	22.72	56 663	29.20	11 321	39.61	6168	43.90	<0.0001

Continued

Table 2. Continued

Variable	Description	No CKD (GFR≥90) (N=163 772)		Mild CKD (60≤GFR<90) (N=279 393)		Moderate CKD (30≤GFR<60) (N=194 030)		Severe CKD (15≤GFR<30) (N=285 83)		Renal Failure (GFR<15) (N=14 049)		*P* Value
Pre-morbid status												
Ambulation	Independent	136 608	83.41	229 396	82.11	150 581	77.61	20 245	70.83	9764	69.50	<0.0001
Symptom type and severity												
Altered Consciousness	Yes	24 012	14.66	47 998	17.18	42 633	21.97	7913	27.68	3879	27.61	<0.0001
NIHSS levels	0-9	80 491	49.15	134 831	48.26	85 084	43.85	11 028	38.58	5299	37.72	
Admission care process												
Door to CT≤25 minutes	Yes	26 861	16.40	54 149	19.38	39 757	20.49	5225	18.28	2027	14.43	<0.0001
Admission biomarkers												
Body mass index, kg/m^2	Mean		28.47 (7.8)		28.04 (7.2)		27.89 (7.2)		28.08 (7.6)		28.13 (8.0)	
Systolic blood pressure (50 to 250 mm Hg)	Mean		156.05 (29.2)		158.36 (29.3)		156.45 (30.9)		151.17 (34.2)		151.66 (35.4)	<0.0001
Serum Creatinine (0 to 20 mg/dL)	Mean		0.72 (0.2)		0.96 (0.2)		1.38 (0.3)		2.56 (0.6)		6.55 (2.7)	
Hospital characteristics												
Number of beds	Mean		471.47 (309.4)		439.62 (297.0)		423.15 (290.2)		428.58 (296)		452.77 (296.1)	<0.0001
Region	West	27 871	17.02	48 663	17.42	32 257	16.62	4541	15.89	2444	17.40	<0.0001
	South	59 701	36.45	99 676	35.68	70 335	36.25	10 764	37.66	5618	39.99	
	Midwest	33 084	20.20	56 647	20.28	40 035	20.63	5849	20.46	2736	19.47	
	Northeast	43 116	26.33	74 407	26.63	51 403	26.49	7429	25.99	3251	23.14	
Hospital type	Academic	107 151	65.43	165 986	59.41	109 036	56.20	16 258	56.88	8448	60.13	<0.0001
Rural location	Yes	6041	3.69	11 169	4.00	8592	4.43	1316	4.60	475	3.38	<0.0001
Avg. annual ischemic stroke cases	Mean		240.20 (146.3)		229.79 (141.1)		223.38 (139.4)		223.40 (140.7)		230.76 (141.7)	

CAD indicates coronary artery disease; CKD, chronic kidney disease; CT, computed tomography; GFR, glomerular filtration rate; MI, myocardial infarction; PVD, peripheral vascular disease; TIA, transient ischemic attack.

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Table 3. Frequencies Comparing Ischemic Stroke Patients With Chronic Kidney Disease (CKD) to Those Without CKD for 7 Performance Measures, a Summary Defect-Free Care Measure, and In-Hospital Outcomes

Variable	Overall (N=679 827)		No CKD (GFR≥60) (N=443 165)		CKD (GFR<60) (N=236 662)		*P* Value
Performance measures	n	%	n	%	n	%	
Patients presenting within 2 hours of ictus receive IV tPA	35 330	78.03	23 039	78.55	12 291	77.08	0.0003
Antithrombotic prescribed within 48 hours of admission	414 672	96.85	263 202	97.12	151 470	96.39	<0.0001
Deep venous thrombosis prophylaxis	322 251	97.50	211 230	97.59	111 021	97.34	<0.0001
Antithrombotic prescribed at discharge	583 330	98.60	390 884	98.66	192 446	98.49	<0.0001
Anticoagulation prescribed at discharge for AF patients	86 199	94.61	51 070	95.05	35 129	93.98	<0.0001
Smoking cessation intervention provided at discharge	112 020	97.12	88 739	97.32	23 281	96.35	<0.0001
Lipid-lowering agent prescribed at discharge	315 999	94.40	209 787	94.60	106 212	94.02	<0.0001
Composite measure							
Defect-free: compliance 100%	590 005	90.81	390 431	91.27	199 574	89.93	<0.0001
In-hospital outcomes							
In-hospital case fatality	32 290	4.75	16 786	3.79	15 504	6.55	<0.0001
In-hospital case fatality or discharged to hospice	61 687	9.07	31 580	7.13	30 107	12.72	<0.0001
Discharge destination other than directly home	314 765	8.61	190 252	44.62	124 513	56.30	<0.0001

AF indicates atrial fibrillation; GFR, glomerular filtration rate.

Table 4. Frequencies Comparing Ischemic Stroke Patients With Various Categories of Chronic Kidney Disease (CKD) to Those Without CKD for 7 Performance Measures, a Summary Defect-Free Care Measure, and In-Hospital Outcomes

Variable	No CKD (GFR≥90) (N=163 772)		Mild CKD (60≤GFR<90) (N=279 393)		Moderate CKD (30≤GFR<60) (N=194 030)		Severe CKD (15≤GFR<30) (N=28 583)		Renal Failure (GFR<15) (N=14 049)		*P* Value
Performance measures	n	%	n	%	n	%	n	%	n	%	
Patients presenting within 2 hours of ictus receive IV tPA	7480	78.21	15 559	78.72	10 678	77.98	1185	73.06	428	67.94	0.0002
Antithrombotic prescribed within 48 hours of admission	96 901	96.97	166 301	97.21	122 656	96.75	19 097	95.22	9717	94.21	<0.0001
Deep venous thrombosis prophylaxis	80 105	97.62	131 125	97.57	91 000	97.40	13 375	97.17	6646	96.82	<0.0001
Antithrombotic prescribed at discharge	146 502	98.55	244 382	98.73	159 897	98.62	21 645	97.92	10 904	97.78	0.0004
Anticoagulation prescribed at discharge for AF patients	13 457	94.78	37 613	95.15	30 423	94.36	3432	91.74	1274	91.20	<0.0001
Smoking cessation intervention provided at discharge	44 581	97.47	44 158	97.17	19 178	96.53	2629	95.81	1474	95.04	<0.0001
Lipid-lowering agent prescribed at discharge	76 542	94.74	133 245	94.51	88 724	94.11	11 998	93.57	5490	93.51	<0.0001
Composite measure											
Defect-free: compliance 100%	145 339	91.37	245 092	91.21	164 938	90.31	23 136	88.42	11 500	87.61	<0.0001
In-hospital outcomes											
In-hospital case fatality	5551	3.39	11 235	4.02	11 451	5.90	2775	9.71	1278	9.10	<0.0001
In-hospital case fatality or discharged to hospice	9842	6.01	21 738	7.78	23 035	11.87	4950	17.32	2122	15.10	<0.0001
Discharge destination other than directly home	65 560	41.44	12 4692	46.50	101 764	55.74	15 811	61.26	6938	54.33	<0.0001

AF indicates atrial fibrillation; GFR, glomerular filtration rate.

Table 5. Unadjusted and Adjusted Odds Ratios Comparing Ischemic Stroke Patients With Various Stages of Kidney Dysfunction to Those With Normal Kidney Function for 7 Performance Measures and a Summary Defect-Free Care Measure

Process Measures	Category of CKD	Unadjusted OR (95% CI)*	*P* Value	Adjusted OR (95% CI)*	*P* Value
Patients presenting within 2 hours of ictus receive IV tPA	CKD (GFR<60)	0.96 (0.93 to 0.99)	0.0158	0.96 (0.91 to 1.01)	0.0903
Patients presenting within 2 hours of ictus receive IV tPA	Mild kidney dysfunction (GFR ≥60 to <90)	1.04 (1.00 to 1.08)	0.0571	1.06 (1.00 to 1.12)	0.0585
Patients presenting within 2 hours of ictus receive IV tPA	Moderate kidney dysfunction (GFR ≥30 to <60)	1.02 (0.97 to 1.07)	0.4550	1.04 (0.97 to 1.11)	0.3105
Patients presenting within 2 hours of ictus receive IV tPA	Severe kidney dysfunction (GFR ≥15 to <30)	0.86 (0.79 to 0.93)	0.0004	0.85 (0.76 to 0.96)	0.0088
Patients presenting within 2 hours of ictus receive IV tPA	Renal failure (GFR<15)	0.74 (0.65 to 0.84)	<0.0001	0.72 (0.61 to 0.85)	0.0001
Deep venous thrombosis prophylaxis	CKD (GFR<60)	0.93 (0.89 to 0.97)	0.0003	0.96 (0.91 to 1.00)	0.0619
Deep venous thrombosis prophylaxis	Mild kidney dysfunction (GFR ≥60 to <90)	1.00 (0.95 to 1.05)	0.9602	1.02 (0.96 to 1.07)	0.6040
Deep venous thrombosis prophylaxis	Moderate kidney dysfunction (GFR ≥30 to <60)	0.95 (0.90 to 1.00)	0.0480	0.98 (0.93 to 1.05)	0.6012
Deep venous thrombosis prophylaxis	Severe kidney dysfunction (GFR ≥15 to <30)	0.89 (0.80 to 0.98)	0.0146	0.94 (0.84 to 1.05)	0.2477
Deep venous thrombosis prophylaxis	Renal failure (GFR<15)	0.79 (0.70 to 0.90)	0.0003	0.83 (0.72 to 0.95)	0.0068
Smoking cessation intervention provided at discharge	CKD (GFR<60)	0.77 (0.73 to 0.82)	<0.0001	0.86 (0.80 to 0.93)	0.0001
Smoking cessation intervention provided at discharge	Mild kidney dysfunction (GFR ≥60 to <90)	0.89 (0.85 to 0.94)	<0.0001	0.95 (0.88 to 1.02)	0.1604
Smoking cessation intervention provided at discharge	Moderate kidney dysfunction (GFR ≥30 to <60)	0.76 (0.71 to 0.81)	<0.0001	0.87 (0.80 to 0.96)	0.0034
Smoking cessation intervention provided at discharge	Severe kidney dysfunction (GFR ≥15 to <30)	0.66 (0.58 to 0.74)	<0.0001	0.76 (0.65 to 0.89)	0.0009
Smoking cessation intervention provided at discharge	Renal failure (GFR<15)	0.59 (0.48 to 0.71)	<0.0001	0.62 (0.48 to 0.78)	0.0001
Antithrombotic prescribed within 48 hours of admission	CKD (GFR<60)	0.80 (0.78 to 0.83)	<0.0001	0.82 (0.79 to 0.85)	<0.0001
Antithrombotic prescribed within 48 hours of admission	Mild kidney dysfunction (GFR ≥60 to <90)	1.05 (1.01 to 1.10)	0.0075	1.08 (1.03 to 1.13)	0.0011
Antithrombotic prescribed within 48 hours of admission	Moderate kidney dysfunction (GFR ≥30 to <60)	0.91 (0.88 to 0.95)	<0.0001	0.96 (0.91 to 1.01)	0.1164
Antithrombotic prescribed within 48 hours of admission	Severe kidney dysfunction (GFR ≥15 to <30)	0.64 (0.60 to 0.69)	<0.0001	0.67 (0.62 to 0.73)	<0.0001
Antithrombotic prescribed within 48 hours of admission	Renal Failure (GFR<15)	0.54 (0.49 to 0.58)	<0.0001	0.54 (0.49 to 0.59)	<0.0001
Antithrombotic prescribed at discharge	CKD (GFR<60)	0.92 (0.89 to 0.95)	<0.0001	0.87 (0.83 to 0.91)	<0.0001
Antithrombotic prescribed at discharge	Mild kidney dysfunction (GFR ≥60 to <90)	1.12 (1.07 to 1.17)	<0.0001	1.08 (1.01 to 1.14)	0.0055
Antithrombotic prescribed at discharge	Moderate kidney dysfunction (GFR ≥30 to <60)	1.06 (1.01 to 1.11)	0.0122	0.98 (0.92 to 1.05)	0.5877
Antithrombotic prescribed at discharge	Severe kidney dysfunction (GFR ≥15 to <30)	0.76 (0.70 to 0.82)	<0.0001	0.68 (0.61 to 0.76)	<0.0001
Antithrombotic prescribed at discharge	Renal Failure (GFR<15)	0.72 (0.65 to 0.81)	<0.0001	0.68 (0.59 to 0.78)	<0.0001
Anticoagulation prescribed at discharge for AF patients	CKD (GFR<60)	0.85 (0.81 to 0.89)	<0.0001	0.90 (0.85 to 0.95)	0.0001

Continued

Table 5. Continued

Process Measures	Category of CKD	Unadjusted OR (95% CI)*	*P* Value	Adjusted OR (95% CI)*	*P* Value
Anticoagulation prescribed at discharge for AF patients	Mild kidney dysfunction (GFR ≥60 to <90)	1.07 (1.01 to 1.14)	0.0222	1.18 (1.09 to 1.27)	<0.0001
Anticoagulation prescribed at discharge for AF patients	Moderate kidney dysfunction (GFR ≥30 to <60)	0.95 (0.89 to 1.01)	0.0908	1.08 (0.99 to 1.18)	0.0737
Anticoagulation prescribed at discharge for AF patients	Severe kidney dysfunction (GFR ≥15 to <30)	0.68 (0.61 to 0.76)	<0.0001	0.76 (0.67 to 0.87)	0.0001
Anticoagulation prescribed at discharge for AF patients	Renal Failure (GFR<15)	0.64 (0.55 to 0.75)	<0.0001	0.64 (0.53 to 0.77)	<0.0001
Lipid-lowering agent prescribed at discharge	CKD (GFR<60)	0.93 (0.91 to 0.95)	<0.0001	0.96 (0.93 to 0.99)	0.0071
Lipid-lowering agent prescribed at discharge	Mild kidney dysfunction (GFR ≥60 to <90)	0.99 (0.96 to 1.02)	0.4052	1.03 (0.99 to 1.07)	0.1256
Lipid-lowering agent prescribed at discharge	Moderate kidney dysfunction (GFR ≥30 to <60)	0.94 (0.90 to 0.97)	0.0002	1.00 (0.96 to 1.05)	0.9794
Lipid to lowering agent prescribed at discharge	Severe kidney dysfunction (GFR ≥15 to <30)	0.87 (0.81 to 0.93)	<0.0001	0.90 (0.83 to 0.97)	0.0068
Lipid-lowering agent prescribed at discharge	Renal Failure (GFR<15)	0.84 (0.77 to 0.92)	0.0001	0.83 (0.74 to 0.92)	0.0003
Defect-free: compliance 100%†	CKD (GFR<60)	0.89 (0.87 to 0.90)	<0.0001	0.91 (0.89 to 0.92)	<0.0001
Defect-free: compliance 100%	Mild kidney dysfunction (GFR ≥60 to <90)	0.99 (0.97 to 1.01)	0.1954	1.00 (0.98 to 1.02)	0.8929
Defect-free: compliance 100%	Moderate kidney dysfunction (GFR ≥30 to <60)	0.91 (0.89 to 0.93)	<0.0001	0.94 (0.92 to 0.97)	<0.0001
Defect-free: compliance 100%	Severe kidney dysfunction (GFR ≥15 to <30)	0.78 (0.75 to 0.81)	<0.0001	0.80 (0.77 to 0.84)	<0.0001
Defect-free: compliance 100%	Renal Failure (GFR<15)	0.73 (0.70 to 0.76)	<0.0001	0.72 (0.68 to 0.76)	<0.0001

CAD indicates coronary artery disease; CKD, Chronic Kidney Disease; GFR, glomerular filtration rate; LDL, low-density lipoprotein; MI, myocardial infarction.
*Compared to normal defined as a glomerular filtration rate≥90. All models are adjusted for age, race, gender, medical history (atrial fibrillation, prosthetic heart valve, previous stroke/TIA, CAD/previous MI, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, heart failure, and current smoking), systolic blood pressure (SBP) at admission, hospital size, region, teaching status, and the number of annual stroke discharges from each hospital. Eligible patients were defined as: (1) if LDL >100 mg/dL; (2) if patient was using lipid-lowering agent at admission; or (3) if LDL was not measured and there were no contraindications to lipid-lowering medications.
†Defect-free care represents the proportion of subjects who received all of the measures that they were eligible for.

compliance; for antithrombotic agents prescribed within 48 hours of admission or at discharge, as well as anticoagulation prescribed at discharge in patients with atrial fibrillation or atrial flutter, those with severe dysfunction and renal failure were less likely to be in compliance, but those with mild dysfunction were more likely to be in compliance; and for defect-free care, those with moderate dysfunction, severe dysfunction, and renal failure were less likely to be in compliance.

Table 6 shows unadjusted and adjusted odds ratios comparing ischemic stroke patients with various stages of kidney dysfunction to those with normal function for the 3 outcome measures. In-hospital case fatality was higher for patients with CKD versus no CKD (adjusted OR 1.44, 95% CI: 1.40 to 1.47), and progressively rose with more severe renal dysfunction to the extent that patients with renal failure had well over twice the odds of dying in the hospital compared to those without CKD (adjusted OR 2.39, 95% CI: 2.22 to 2.57). Presence of CKD (versus no CKD) was also associated with poorer outcomes with regard to the endpoints of in-hospital case fatality or discharged to hospice (adjusted OR 1.31, 95% CI: 1.28 to 1.33) and discharge destination other than directly home (adjusted OR 1.06, 95% CI: 1.04 to 1.07). However, analyses by stage of renal dysfunction showed that patients with earlier stages of dysfunction had better outcomes than those with normal function: patients with mild dysfunction had lower odds of experiencing in-hospital case fatality or being discharged to hospice (adjusted OR 0.88, 95% CI: 0.85 to 0.91), and those with mild dysfunction (adjusted OR 0.81, 95% CI: 0.80 to 0.83) or moderate dysfunction (adjusted OR 0.88, 95% CI: 0.86 to 0.90) had lower odds of discharge destination other than home. The more advanced stages of renal dysfunction (severe and failure) were both associated with higher odds of experiencing in-hospital case fatality/

Table 6. Unadjusted and Adjusted Odds Ratios Comparing Ischemic Stroke Patients With Various Stages of Kidney Dysfunction to Those With Normal Kidney Function for 3 Outcome Measures

Outcome Measures	Category of CKD	Unadjusted OR (95% CI)*	*P* Value	Adjusted OR (95% CI)*	*P* Value
In-hospital case fatality	CKD (GFR<60)	1.90 (1.85 to 1.95)	<0.0001	1.44 (1.40 to 1.47)	<0.0001
In-hospital case fatality	Mild kidney dysfunction (GFR ≥60 to <90)	1.28 (1.23 to 1.33)	<0.0001	0.99 (0.95 to 1.03)	0.5626
In-hospital case fatality	Moderate kidney dysfunction (GFR ≥30 to <60)	1.99 (1.91 to 2.08)	<0.0001	1.27 (1.22 to 1.32)	<0.0001
In-hospital case fatality	Severe kidney dysfunction (GFR ≥15 to <30)	3.45 (3.27 to 3.65)	<0.0001	2.14 (2.03 to 2.26)	<0.0001
In-hospital case fatality	Renal failure (GFR<15)	3.16 (2.94 to 3.41)	<0.0001	2.39 (2.22 to 2.57)	<0.0001
In-hospital case fatality or discharged to hospice	CKD (GFR<60)	1.94 (1.91 to 1.98)	<0.0001	1.31 (1.28 to 1.33)	<0.0001
In-hospital case fatality or discharged to hospice	Mild kidney dysfunction (GFR ≥60 to <90)	1.35 (1.31 to 1.38)	<0.0001	0.88 (0.85 to 0.91)	<0.0001
In-hospital case fatality or discharged to hospice	Moderate kidney dysfunction (GFR ≥30 to <60)	2.19 (2.12 to 2.25)	<0.0001	1.07 (1.04 to 1.11)	<0.0001
In-hospital case fatality or discharged to hospice	Severe kidney dysfunction (GFR ≥15 to <30)	3.43 (3.30 to 3.56)	<0.0001	1.70 (1.63 to 1.78)	<0.0001
In-hospital case fatality or discharged to hospice	Renal failure (GFR<15)	2.91 (2.75 to 3.09)	<0.0001	2.09 (1.96 to 2.23)	<0.0001
Discharge destination other than directly home	CKD (GFR<60)	1.60 (1.58 to 1.62)	<0.0001	1.06 (1.04 to 1.07)	<0.0001
Discharge destination other than directly home	Mild kidney dysfunction (GFR ≥60 to <90)	1.23 (1.21 to 1.25)	<0.0001	0.81 (0.80 to 0.83)	<0.0001
Discharge destination other than directly home	Moderate kidney dysfunction (GFR ≥30 to <60)	1.78 (1.74 to 1.82)	<0.0001	0.88 (0.86 to 0.90)	<0.0001
Discharge destination other than directly home	Severe kidney dysfunction (GFR ≥15 to <30)	2.24 (2.17 to 2.31)	<0.0001	1.10 (1.07 to 1.14)	<0.0001
Discharge destination other than directly home	Renal failure (GFR<15)	1.68 (1.61 to 1.75)	<0.0001	1.11 (1.06 to 1.16)	<0.0001

CAD indicates coronary artery disease; CKD, chronic kidney disease; GFR, glomerular filtration rate; LDL, low-density lipoprotein; MI, myocardial infarction.
*Compared to normal defined as a glomerular filtration rate≥90. All models are adjusted for age, race, gender, medical history (atrial fibrillation, prosthetic heart valve, previous stroke/TIA, CAD/previous MI, carotid stenosis, peripheral vascular disease, hypertension, dyslipidemia, heart failure, and current smoking), systolic blood pressure (SBP) at admission, hospital size, region, teaching status, and the number of annual stroke discharges from each hospital.

being discharged to hospice and a discharge destination other than home (Table 6). Regression models that included the measure of stroke severity (NIH Stroke Scale Score) showed a similar pattern of results (not shown).

Discussion

In this large, contemporary nationwide study, we observed that 1 of every 3 hospitalized ischemic stroke patients had CKD, that the odds of dying in the hospital after adjusting for major confounders was 44% higher for those patients with CKD compared with those without CKD, and the independent relation of kidney dysfunction with in-hospital mortality rose progressively with worsening renal dysfunction. These results, based on >600 000 ischemic stroke admissions at >1500 hospitals, definitively confirm data from previously published analyses of small single-center studies that showed a high prevalence of CKD linked to poorer outcomes among hospitalized ischemic stroke patients. In addition, our study is the first as far as we are aware to evaluate the quality of stroke-related care among hospitalized ischemic stroke patients by CKD presence and stage of kidney dysfunction, finding that patients with evidence of renal dysfunction are significantly less likely to receive several effective therapies, which are currently included in ischemic stroke hospitalization performance and quality measures. This latter finding is in accord with studies among patients hospitalized with acute cardiovascular conditions that revealed greater underuse of medications for vascular risk reduction as kidney function declines.[13–15]

A major strength of our study was the ability to also examine the relationships of specific stages of kidney dysfunction to various stroke hospitalization performance measures and in-hospital outcome types. For instance, while the overriding message from our results is that presence of CKD is associated with lesser compliance with benchmarks of stroke care and poorer outcomes, these results were primarily driven by the more advanced stages of dysfunction, ie, severe and failure. Indeed, hospitalized ischemic stroke patients with mild dysfunction actually had similar or better in-hospital outcomes when compared with those patients with normal function. On the surface, this may seem counterintuitive since proposed explanations for why vascular disease patients with CKD may have poorer clinical outcomes than those without CKD, is the frequent co-presence in the former patient group of deleterious conditions like anemia, oxidative stress, electrolyte imbalances, hyperhomocysteinemia, and chronic inflammation.[16] However, in our study we observed that patients with mild dysfunction versus normal function were significantly more likely to receive an antithrombotic prescription within 48 hours of admission, be discharged on an antithrombotic, receive anticoagulation at discharge if they had a diagnosis of atrial fibrillation or flutter; showed a strong trend towards being more likely to receive intravenous thrombolysis; showed a non-significant pattern of being more likely to receive a lipid-lowering agent at discharge; and were no less likely to receive smoking cessation counseling at discharge, deep venous thrombosis prophylaxis, or overall stroke hospitalization defect-free care. Although given the nature of our study, we could not establish causality, it is not inconceivable that better in-hospital care and perhaps significantly higher frequency of pre-morbid cardiovascular medications in patients with mild CKD versus normal function may have led to similar or better outcomes among the former patient group.

Underutilization of evidence-based treatments has similarly been seen in other patient subgroups with chronic conditions that place them at high vascular risk such as diabetes mellitus and peripheral artery disease.[17,18] While the specific reasons for why there is an underuse of evidence-based therapies among hospitalized ischemic patients with CKD are not exactly known, it stands to reason that potential contributors to this evidence-practice treatment gap may include the facts that the randomized trial evidence upon which several expert-consensus recommendations for stroke treatment are based typically excluded patients with major renal dysfunction,[9,10] patients with CKD are generally more likely to experience adverse effects of many medications,[19] given the effect of renal azotemia on platelet function patients with kidney disease are at an increased risk for bleeding,[20] and questionable therapeutic efficacy.[21,22] All of the aforementioned factors may be leading clinicians caring for hospitalized ischemic stroke patients to be more cautious about prescribing these therapies, despite the greater risk for cardiovascular events and poor clinical outcomes in these patients.[2–6] However, emerging evidence suggests that the benefits of many secondary prevention drugs used in the treatment of known vascular disease may be of equal or greater benefit to those with renal dysfunction when compared with those without,[19] and a published analysis of the GWTG-Stroke dataset that looked at predictors of tPA-related sICH did not find any association between serum creatinine levels and risk for tPA-related sICH.[23]

This study has limitations. First, data were derived from the medical record and depended on the accuracy and completeness of clinical documentation (eg, it is conceivable that some patients reported to be eligible for treatment were not treated due to contraindications or intolerance that was not documented; or very ill patients with advanced CKD in the process of being discharged to hospice for terminal care were not candidates for certain treatments). Second, although hospitals are instructed to include all consecutive admissions or to take a random sample, these processes are not audited so the potential for selection bias exists. Third, while we controlled for known confounders, unmeasured confounding could have affected our results. Fourth, our findings may not necessarily apply to hospitals that differ in patient characteristics or care patterns from GWTG-Stroke hospitals. Fifth, we only examined in-hospital outcomes, therefore, the longer-term impact of CKD or of the differences in quality of care identified in this study on stroke-related outcomes were not determined. Next, although the MDRD formula is the preferred method for estimating renal function, it generally should be applied when renal function is stable, and this may not be the case for many patients admitted with acute ischemic stroke, potentially limiting its usefulness in this population. 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 acute ischemic stroke. In addition, admission creatinine was not available in all patients, which may have introduced bias into the findings. Finally, we were unable to definitively establish an association between hospital care performance measures and outcomes or pinpoint the mechanisms by which renal dysfunction may affect mortality.

In conclusion, in this sizeable multi-site study we confirmed that renal dysfunction prevalence is high and associated with poor clinical outcomes among patients hospitalized with an ischemic stroke. Furthermore, we found that despite higher rates of in-hospital mortality linked to worsening renal dysfunction, ischemic stroke patients with advanced stages of dysfunction were significantly less likely to receive evidence-based pharmacologic and non-pharmacologic management strategies during their index hospitalization.

Intensified quality improvement efforts are warranted to enhance the care of hospitalized patients with ischemic stroke and kidney dysfunction.

Author Contributions

All authors were involved in the final decision to submit the manuscript. *Study concept and design:* Ovbiagele, Fonarow. *Acquisition of data:* Get With The Guidelines Stroke Personnel. *Analysis and interpretation of data:* Ovbiagele, Schwamm, Smith, Grau-Sepulveda, Saver, Bhatt, Hernandez, Peterson, Fonarow. *Drafting of the manuscript:* Ovbiagele. *Critical revision of the manuscript for important intellectual content:* Ovbiagele, Schwamm, Smith, Grau-Sepulveda, Saver, Bhatt, Hernandez, Peterson, Fonarow. *Statistical analysis:* Grau-Sepulveda.

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