Chronic kidney disease (CKD) is highly prevalent among hospitalized patients with stroke and is an independent predictor of poor clinical outcomes in these patients. Although intravenous tissue-type plasminogen activator (IV tPA) can reverse the damaging consequences of acute ischemic stroke (AIS), 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, and IV tPA is associated with an increased risk of symptomatic intracranial hemorrhage (sICH).

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
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.

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 continuous quality improvement of hospital systems of care for patients with 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, procedures, and discharge characteristics. Although the GWTG-Stroke program is oversampled with larger academic teaching hospitals, the patient demographics and comorbidities are similar to those described in other stroke registries and administrative databases. 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)−1.15 4×age−0.20×(0.742 if female)×(1.21 if black). 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). 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 neurologically 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. 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 χ² 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. 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal Function (GFR≥90) (N=9788)</th>
<th>Mild CKD (GFR≥60 to &lt;90) (N=19431)</th>
<th>Moderate CKD (GFR≥30 to &lt;60) (N=13097)</th>
<th>Severe CKD (GFR≥15 to &lt;30) (N=1516)</th>
<th>Renal Failure (GFR&lt;15) (N=578)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age, y SD</td>
<td>60.60</td>
<td>69.76</td>
<td>76.78</td>
<td>77.39</td>
<td>68.37</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female sex, n (%)</td>
<td>4092</td>
<td>9176</td>
<td>7984</td>
<td>976</td>
<td>323</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>White race, n (%)</td>
<td>6147</td>
<td>14288</td>
<td>10166</td>
<td>1105</td>
<td>322</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Black race, n (%)</td>
<td>2143</td>
<td>2639</td>
<td>1386</td>
<td>220</td>
<td>154</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hispanic ethnicity, n (%)</td>
<td>907</td>
<td>1266</td>
<td>795</td>
<td>60</td>
<td>64</td>
<td>0.0579</td>
</tr>
<tr>
<td>Arrival information</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMS arrival from home/scene, n (%)</td>
<td>7423</td>
<td>15576</td>
<td>11068</td>
<td>1308</td>
<td>468</td>
<td>0.097</td>
</tr>
<tr>
<td>Median LKW to arrival in minutes; 25th, 75th percentile</td>
<td>61</td>
<td>40</td>
<td>97</td>
<td>59</td>
<td>39</td>
<td>90</td>
</tr>
<tr>
<td>Past medical history, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fib/flutter</td>
<td>1134</td>
<td>3999</td>
<td>2669</td>
<td>442</td>
<td>134</td>
<td>0.0001</td>
</tr>
<tr>
<td>CAD/prior MI</td>
<td>1794</td>
<td>4597</td>
<td>4220</td>
<td>584</td>
<td>191</td>
<td>0.0001</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>152</td>
<td>502</td>
<td>478</td>
<td>64</td>
<td>9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2291</td>
<td>4345</td>
<td>3859</td>
<td>672</td>
<td>296</td>
<td>0.0001</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>3211</td>
<td>7802</td>
<td>6001</td>
<td>692</td>
<td>225</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6042</td>
<td>13857</td>
<td>10797</td>
<td>1318</td>
<td>491</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Prosthetic heart valve</td>
<td>9</td>
<td>210</td>
<td>171</td>
<td>23</td>
<td>3</td>
<td>0.0579</td>
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<tr>
<td>Peripheral vascular Dx</td>
<td>192</td>
<td>570</td>
<td>578</td>
<td>119</td>
<td>45</td>
<td>0.0001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>444</td>
<td>1417</td>
<td>1706</td>
<td>326</td>
<td>114</td>
<td>0.0001</td>
</tr>
<tr>
<td>Active smoking</td>
<td>2895</td>
<td>3441</td>
<td>1462</td>
<td>155</td>
<td>73</td>
<td>0.0001</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>2064</td>
<td>4647</td>
<td>3605</td>
<td>451</td>
<td>164</td>
<td>0.0001</td>
</tr>
<tr>
<td>Independent ambulation</td>
<td>8570</td>
<td>16702</td>
<td>10811</td>
<td>1169</td>
<td>452</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Premorbid medications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>551</td>
<td>1440</td>
<td>1117</td>
<td>114</td>
<td>53</td>
<td>0.0001</td>
</tr>
<tr>
<td>Antiplatlets</td>
<td>3292</td>
<td>8320</td>
<td>6741</td>
<td>817</td>
<td>273</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>5024</td>
<td>12649</td>
<td>10597</td>
<td>1326</td>
<td>468</td>
<td>0.0001</td>
</tr>
<tr>
<td>Cholesterol reducers</td>
<td>2926</td>
<td>7452</td>
<td>6170</td>
<td>796</td>
<td>267</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Antidiabetic drugs</td>
<td>1712</td>
<td>3337</td>
<td>3021</td>
<td>484</td>
<td>181</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Admission information</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered consciousness, n (%)</td>
<td>1431</td>
<td>3339</td>
<td>2688</td>
<td>354</td>
<td>125</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median NIHSS, 25th, 75th percentile</td>
<td>9</td>
<td>10</td>
<td>12</td>
<td>12</td>
<td>11</td>
<td>0.0001</td>
</tr>
<tr>
<td>Door to computed tomography ≤25 min, n (%)</td>
<td>5749</td>
<td>58.74</td>
<td>11986</td>
<td>8094</td>
<td>921</td>
<td>60.75</td>
</tr>
<tr>
<td>Mean BMI (SD), kg/m²</td>
<td>28.91</td>
<td>28.32</td>
<td>28.16</td>
<td>28.04</td>
<td>27.82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean systolic blood pressure (SD), mmHg</td>
<td>154.73</td>
<td>27.75</td>
<td>157.46</td>
<td>157.70</td>
<td>155.49</td>
<td>31.27</td>
</tr>
<tr>
<td>Mean serum creatinine (SD), mg/dL</td>
<td>0.74</td>
<td>0.15</td>
<td>0.17</td>
<td>1.36</td>
<td>0.29</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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.
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 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 sICH and SSH 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

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall (N=44410)</th>
<th>No CKD (GFR≥90) (N=29219)</th>
<th>CKD (GFR&lt;60) (N=15191)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic intracranial hemorrhage</td>
<td>2053</td>
<td>4.62</td>
<td>1229</td>
<td>4.21</td>
</tr>
<tr>
<td>Serious systemic hemorrhage</td>
<td>441</td>
<td>0.99</td>
<td>260</td>
<td>0.89</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>3528</td>
<td>7.94</td>
<td>1898</td>
<td>6.50</td>
</tr>
<tr>
<td>No independent ambulation at discharge</td>
<td>20034</td>
<td>49.00</td>
<td>12318</td>
<td>45.09</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall (N=44410)</th>
<th>Normal Function (GFR≥90) (N=9788)</th>
<th>Mild CKD (GFR≥60 to &lt;90) (N=19431)</th>
<th>Moderate CKD (GFR≥30 to &lt;60) (N=13097)</th>
<th>Severe CKD (GFR≥15 to &lt;30) (N=1516)</th>
<th>Renal Failure (GFR&lt;15) (N=578)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic intracranial hemorrhage</td>
<td>2053</td>
<td>4.62</td>
<td>327</td>
<td>3.34</td>
<td>902</td>
<td>4.64</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serious systemic hemorrhage</td>
<td>441</td>
<td>0.99</td>
<td>67</td>
<td>0.68</td>
<td>193</td>
<td>0.99</td>
<td>0.0032</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>3528</td>
<td>7.94</td>
<td>482</td>
<td>4.92</td>
<td>1416</td>
<td>7.29</td>
<td>17</td>
</tr>
<tr>
<td>No independent Ambulation at discharge</td>
<td>20034</td>
<td>49.00</td>
<td>3862</td>
<td>41.50</td>
<td>8456</td>
<td>46.94</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

CKD indicates chronic kidney disease; and GFR, glomerular filtration rate.
ischemic stroke, may be more likely because of the co-presence (with CKD) of other harmful conditions like anemia, oxidative stress, electrolyte imbalances, and chronic inflammation, rather than the abnormalities in coagulation and platelet function typically associated with CKD. 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.

Data from previously published studies that have examined this issue were based on patient populations numbering less than a 1000 and revealed differing results. 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, a study of 740 patients in Germany revealed that only severe renal impairment was associated with sICH after IV tPA treatment, 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, 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. 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. A sixth study (n=229) found that patients with ischemic stroke treated with IV tPA who had renal dysfunction

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)

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

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.
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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

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)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CKD Categorization</th>
<th>Category of CKD</th>
<th>Unadjusted OR (95% CI)</th>
<th>P Value</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic intracranial hemorrhage</td>
<td>Dichotomous</td>
<td>CKD (GFR&lt;60)</td>
<td>1.30 (1.18–1.43)</td>
<td>&lt;0.0001</td>
<td>0.99 (0.89–1.09)</td>
<td>0.7767</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mild dysfunction</td>
<td>1.39 (1.22–1.58)</td>
<td>&lt;0.0001</td>
<td>1.08 (0.94–1.24)</td>
<td>0.2525</td>
</tr>
<tr>
<td></td>
<td>Polytomous</td>
<td>Moderate dysfunction</td>
<td>1.69 (1.48–1.94)</td>
<td>&lt;0.0001</td>
<td>1.08 (0.93–1.26)</td>
<td>0.2941</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe dysfunction</td>
<td>1.50 (1.15–1.95)</td>
<td>0.0028</td>
<td>0.92 (0.70–1.21)</td>
<td>0.5385</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal failure (GFR&lt;15)</td>
<td>0.83 (0.49–1.39)</td>
<td>0.2474</td>
<td>0.60 (0.35–1.03)</td>
<td>0.0628</td>
</tr>
<tr>
<td>Severe systemic hemorrhage</td>
<td>Dichotomous</td>
<td>CKD (GFR&lt;60)</td>
<td>1.40 (1.15–1.70)</td>
<td>0.0006</td>
<td>0.97 (0.79–1.19)</td>
<td>0.7819</td>
</tr>
<tr>
<td></td>
<td>Polytomous</td>
<td>Mild dysfunction</td>
<td>1.69 (1.26–2.26)</td>
<td>0.0005</td>
<td>1.22 (0.90–1.65)</td>
<td>0.1914</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate dysfunction</td>
<td>2.05 (1.53–2.73)</td>
<td>&lt;0.0001</td>
<td>1.14 (0.84–1.56)</td>
<td>0.3999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe dysfunction</td>
<td>2.03 (1.20–3.42)</td>
<td>0.0082</td>
<td>1.05 (0.61–1.63)</td>
<td>0.8519</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal failure (GFR&lt;15)</td>
<td>1.87 (0.82–4.28)</td>
<td>0.1358</td>
<td>1.25 (0.54–2.88)</td>
<td>0.5964</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>Dichotomous</td>
<td>Any CKD (GFR&lt;60)</td>
<td>1.74 (1.61–1.88)</td>
<td>&lt;0.0001</td>
<td>1.19 (1.09–1.30)</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Polytomous</td>
<td>Mild CKD (GFR&gt;60 to &lt;90)</td>
<td>1.53 (1.36–1.71)</td>
<td>&lt;0.0001</td>
<td>1.10 (0.97–1.24)</td>
<td>0.1301</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate CKD (GFR&gt;60 to &lt;90)</td>
<td>2.22 (1.97–2.50)</td>
<td>&lt;0.0001</td>
<td>1.20 (1.05–1.38)</td>
<td>0.0064</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe CKD (GFR&gt;15 to &lt;30)</td>
<td>3.20 (2.66–3.85)</td>
<td>&lt;0.0001</td>
<td>1.66 (1.35–2.04)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal failure (GFR&lt;15)</td>
<td>3.10 (2.38–4.06)</td>
<td>&lt;0.0001</td>
<td>2.21 (1.65–2.96)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lack of independent ambulation at discharge</td>
<td>Dichotomous</td>
<td>Any CKD (GFR&lt;60)</td>
<td>1.82 (1.73–1.91)</td>
<td>&lt;0.0001</td>
<td>1.13 (1.07–1.19)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Polytomous</td>
<td>Mild CKD (GFR&gt;60 to &lt;90)</td>
<td>1.31 (1.24–1.39)</td>
<td>&lt;0.0001</td>
<td>0.88 (0.82–0.94)</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate CKD (GFR&gt;60 to &lt;90)</td>
<td>2.13 (1.99–2.27)</td>
<td>&lt;0.0001</td>
<td>1.00 (0.92–1.08)</td>
<td>0.9047</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe CKD (GFR&gt;15 to &lt;30)</td>
<td>2.96 (2.56–3.41)</td>
<td>&lt;0.0001</td>
<td>1.29 (1.10–1.52)</td>
<td>0.0019</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Renal failure (GFR&lt;15)</td>
<td>1.81 (1.48–2.20)</td>
<td>&lt;0.0001</td>
<td>1.21 (0.98–1.49)</td>
<td>0.0697</td>
</tr>
</tbody>
</table>

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.
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.

Sources of Funding

The Get With the Guidelines Program is funded by the American Heart Association and the American Stroke Association. The program is also supported, in part, by unrestricted educational grants to the American Heart Association by Pfizer (New York, NY) and the Merck-Schering Plough Partnership (North Wales, PA), who did not participate in the design, analysis, or article preparation and did not require approval of this article for submission.

Disclosures

Dr Schwamm reports serving as Get With the Guidelines Program (GWTG)-Stroke Clinical Workgroup Chair, being principal investigator of the National Institute of Neurological Disorders and Stroke/Genentech funded Phase IIa Safety Study of Intravenous Thrombolysis with Alteplase in MRI-Selected Patients (MR WITNESS) study if extended window thrombolysis, and serving as a member of the International Steering Committee for DIAS3/4 Lundbeck. Dr Saver reports serving as a member of the GWTG Steering Committee, receipt of research support (to the institution) from National Institutes of Health (NIH), and being an employee of the University of California which holds a patent on retriever devices. Dr Bhatt reports Advisory Board: Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Get With The Guidelines Steering Committee; Honoraria: American College of Cardiology (Editor, Clinical Trials, Cardiosource), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Population Health Research Institute (clinical trial steering committees), Slack Publications (Chief Medical Editor, Cardiology Today’s Intervention), WebMD (CMER steering committees); other: Senior Associate Editor, Journal of Invasive Cardiology; Data Monitoring Committees: Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Population Health Research Institute; research grants: Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic, Sanofi Aventis, The Medicines Company; and unfunded research: FlowCo, PLx Pharma, Takeda. Dr Fonarow reports serving as a member of the GWTG Steering Committee, receipt of research support (to the institution) from NIH and from Patient-Centered Outcomes Research Institute, and being an employee of the University of California which holds a patent on retriever devices. The other authors report no conflicts.

References

Chronic Kidney Disease and Bleeding Complications After Intravenous Thrombolytic Therapy for Acute Ischemic Stroke
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Circ Cardiovasc Qual Outcomes. 2014;7:929-935; originally published online September 23, 2014;
doi: 10.1161/CIRQOUTCOMES.114.001144
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7705. Online ISSN: 1941-7713

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