Adults With Late Stage 3 Chronic Kidney Disease Are at High Risk for Prevalent Silent Brain Infarction
A Population-Based Study

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Background and Purpose—The close relationship between stroke and chronic kidney disease (CKD) has been well-documented. However, few studies have focused on silent brain infarction (SBI) in CKD. We investigated the prevalence of SBI in different stages of CKD.

Methods—We included 1312 participants aged 30 to 93 years who came from either a random sample of residents or from a group of physically examined subjects in the same community. Basic information, clinical evaluations, laboratory tests, and MRI images were assessed. Subjects were divided into groups 1, 2, 3a, and 3b, corresponding to the estimated glomerular filtration rate (eGFR) levels of ≥90.0, 60.0 to 89.9, 45.0 to 59.9, and 30.0 to 44.9 mL/min/1.73 m².

Results—The crude prevalence was 4.7%: 2.6% (20 of 759 subjects) in group 1; 6.3% (32 of 506) in group 2; 12.9% (4 of 31) in group 3a; and 37.5% (6 of 16) in group 3b (P<0.001). Additionally, SBI also correlated with age, male sex, hypertension, diabetes, moderate carotid plaque, higher blood pressures, obesity, and levels of triglyceride, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and uric acid (all P<0.05). The effects for SBI risk in each eGFR group versus group 1 did not increase except for group 3b (OR, 9.34; P<0.001).

Conclusions—A close association exists between SBI and eGFR. We have found a significant increase in prevalence of SBI when eGFR is between 30.0 and 44.9 mL/min/1.73 m². Adults with late stage 3 CKD are at high risk for prevalent SBI. (Stroke. 2011;42:00-00.)

Key Words: chronic kidney disease ■ magnetic resonance imaging ■ silent brain infarction

Silent brain infarction (SBI) is a type of cerebral infarction that can be identified radiologically but that has no clinical symptoms. SBI is a lacunar infarction caused by the occlusion of small penetrating cerebral arteries, which differs from large vessel diseases such as coronary heart disease. The presence of SBI has been considered as a strong predictor for clinical overt stroke. The close relationship between chronic kidney disease (CKD) and the high risk of stroke and other cardiovascular diseases has been well-documented. Some reports have shown that the prevalent SBI can predict vascular events in end-stage renal disease patients. Recently, the relationship between CKD and SBI has been noticed by some authors. The majority of authors agree that a significant inverse relationship exists between estimated glomerular filtration rate (eGFR) and the presence of SBI. However, in these studies most of the subjects were those with an eGFR <60 mL/min/1.73 m², outpatients, or people older than 60 years old. The composition of these subjects was far different from that of the population as a whole. No study has addressed the risk of SBI in people of the general population with an eGFR ≥60 mL/min/1.73 m² or CKD stage 1 and 2. There was no community study about the relationship of SBI and CKD.

The loss of microvasculature is critical for progressive renal disease. The expression of many growth factors and cytokines such as platelet-derived growth factor, tumor necrosis factor-α, and transforming growth factor-β in endothelium can be observed in both of progressive renal and systemic atherosclerotic microvasculature. We suppose that small cerebral vessel abnormalities, as those found in SBI, occur in the early stage of CKD. Therefore, our goal was to examine the prevalence of SBI in different stages of CKD in adults.

Materials and Methods

Participants
A total of 1404 participants were recruited since November 2003 to November 2005. All of them resided in Taipei City. They came from...
Table 1. Demographic and Clinical Characteristics by the Glomerular Filtration Rate Groups

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>1 (≥90.0)</th>
<th>2 (60.0–89.9)</th>
<th>3a (45.0–59.9)</th>
<th>3b (30.0–44.9)</th>
<th>P₁</th>
<th>P₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>1312</td>
<td>759</td>
<td>506</td>
<td>31</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with silent brain infarction</td>
<td>62</td>
<td>20</td>
<td>32</td>
<td>4</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>765 (58.3)</td>
<td>372 (49.0)</td>
<td>358 (70.8)</td>
<td>23 (74.2)</td>
<td>11 (68.8)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (y)</td>
<td>52.5±10.0</td>
<td>50.2±8.5</td>
<td>55.1±10.8</td>
<td>61.4±10.6</td>
<td>64.4±9.1</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>276 (21.0)</td>
<td>141 (18.6)</td>
<td>117 (23.1)</td>
<td>12 (38.7)</td>
<td>6 (37.5)</td>
<td>0.006</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
<td>193 (14.7)</td>
<td>100 (13.2)</td>
<td>77 (15.2)</td>
<td>9 (29.0)</td>
<td>6 (37.5)</td>
<td>0.0004</td>
<td>0.002</td>
</tr>
<tr>
<td>Carotid plaque score ≥4 (%)</td>
<td>137 (10.4)</td>
<td>49 (6.5)</td>
<td>73 (14.4)</td>
<td>10 (32.3)</td>
<td>4 (25.0)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of cardiovascular disease (%)</td>
<td>66 (5.0)</td>
<td>37 (4.9)</td>
<td>26 (5.1)</td>
<td>1 (3.2)</td>
<td>2 (12.5)</td>
<td>0.546</td>
<td>0.266</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>3 (0.23)</td>
<td>1 (0.13)</td>
<td>2 (0.40)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0.793</td>
<td>0.287</td>
</tr>
<tr>
<td>Past and current smoking habit (%)</td>
<td>493 (37.6)</td>
<td>267 (35.2)</td>
<td>207 (41.0)</td>
<td>14 (45.2)</td>
<td>5 (31.2)</td>
<td>0.149</td>
<td>0.040</td>
</tr>
<tr>
<td>Alcohol drinking habit (%)</td>
<td>385 (29.3)</td>
<td>221 (29.2)</td>
<td>153 (30.2)</td>
<td>9 (29.0)</td>
<td>2 (12.5)</td>
<td>0.494</td>
<td>0.349</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>123.1±10.6</td>
<td>121.2±20.6</td>
<td>124.8±19.5</td>
<td>136.4±26.8</td>
<td>133.5±23.7</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>73.7±11.7</td>
<td>72.8±11.9</td>
<td>74.5±11.0</td>
<td>78.7±12.6</td>
<td>77.2±14.6</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>24.7±3.3</td>
<td>24.5±3.4</td>
<td>24.8±3.0</td>
<td>26.4±4.1</td>
<td>25.9±3.5</td>
<td>0.006</td>
<td>0.003</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>207.4±37.1</td>
<td>204.6±35.5</td>
<td>211.1±33.2</td>
<td>214.0±54.0</td>
<td>214.0±31.9</td>
<td>0.013</td>
<td>0.002</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>138.6±78.8</td>
<td>135.8±81.7</td>
<td>139.3±72.4</td>
<td>155.0±90.5</td>
<td>208.2±85.2</td>
<td>0.002</td>
<td>0.006</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>53.1±14.7</td>
<td>54.2±15.5</td>
<td>52.0±13.2</td>
<td>49.5±14.4</td>
<td>48.4±14.0</td>
<td>0.013</td>
<td>0.001</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dL</td>
<td>121.2±30.6</td>
<td>117.5±29.3</td>
<td>126.2±31.2</td>
<td>127.9±39.6</td>
<td>125.1±25.4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein, mg/dL*</td>
<td>0.10±0.20</td>
<td>0.10±0.19</td>
<td>0.10±0.20</td>
<td>0.16±0.27</td>
<td>0.24±0.23</td>
<td>0.027</td>
<td>0.007</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>6.2±1.6</td>
<td>5.8±1.4</td>
<td>6.7±1.6</td>
<td>7.8±1.8</td>
<td>7.6±2.0</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin, mg/dL</td>
<td>14.4±1.5</td>
<td>14.2±1.5</td>
<td>14.7±1.4</td>
<td>14.3±2.0</td>
<td>13.4±1.8</td>
<td>&lt;0.001</td>
<td>0.004</td>
</tr>
<tr>
<td>Albumin, mg/dL</td>
<td>4.55±0.27</td>
<td>4.54±0.26</td>
<td>4.55±0.27</td>
<td>4.53±0.31</td>
<td>4.42±0.13</td>
<td>0.710</td>
<td>0.862</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.86±0.23</td>
<td>0.72±0.13</td>
<td>0.98±0.14</td>
<td>1.35±0.19</td>
<td>1.76±0.29</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, mL/min/1.73 m²</td>
<td>93.8±20.2</td>
<td>106.9±14.5</td>
<td>78.6±7.3</td>
<td>53.7±4.3</td>
<td>38.7±4.4</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

P₁ indicates ANOVA test; P₂ trend test.

Data expressed by mean±standard deviation, *median (interquartile range), or frequency (percent).

2 population sources. The first (n=535) was a random sample from the community. These participants were residents in the community neighboring Shin Kong Wu Ho-Su Memorial Hospital and were randomly chosen from all residents older than age 30 years. They were invited to a community-based prospective cohort study investigating the cardiovascular and cerebrovascular risk factors in general population. Details of the sampling scheme and descriptions have been published elsewhere. Subjects of the second group (n=869) were volunteers in the same community. They agreed to join our study and receive an additional neurological examination during their self-paid physical examination in Shin Kong Wu Ho-Su Memorial Hospital. All participants were examined at the Wellness Center of Shin Kong Wu Ho-Su Memorial Hospital. Those who had had a self-reported or diagnostic stroke (n=68), current episode of fever (n=23), or eGFR <30 mL/min/1.73 m² (n=1) were excluded; therefore, 1312 participants were included. The ethical committee of Shin Kong Wu Ho-Su Memorial Hospital approved our study. All participants signed an informed consent form.

Data Collection and Measurements

Clinical Evaluations

A standardized and structured questionnaire, completed by well-trained interviewers, was used to gather information about a subject’s history of cardiovascular disease or stroke, current medication for hypertension or diabetes control, and smoking and alcohol habits. Demographic information was collected. At the same time, a physical examination was performed by neurologists. Having a history of cardiovascular disease or stroke was defined as having any diagnosis of coronary artery disease, angina pectoris, myocardial infarction, or clinical overt cerebral infarction informed by clinicians in the past. Blood pressure (BP) was measured with a validated oscillometric automated digital blood pressure device (OMRON HEM-757; Omron Matsusaka). Body height and weight were measured by a validated automated device (TBF-22; TANITA), and then body mass index was calculated.

Specimen Collection

Our participants were asked to fast overnight (≥8 hours). The blood samples were analyzed using colorimetry by an automatic chemistry analyzer (UniCel DxC 800; Beckman Coulter). Levels of hemoglobin, serum total cholesterol, triglyceride, high-density lipoprotein cholesterol, creatinine, glucose, high-sensitivity C-reactive protein, uric acid, and albumin were assessed in an approved laboratory. The low-density lipoprotein cholesterol level was calculated using the Friedewald formula.

Neurological Assessment and Identification

A color-coded and duplex Doppler sonography system (SONOs 1000; Hewlett-Packard) and a whole-brain MRI scan (1.5T AVANTO; Siemens) were performed by well-trained technologists. All sonographic readings were scored by a neurological technician who was blind to individual profiles. The degree of carotid plaque was graded from 0 to 3 in each segment of common, internal, and external carotid arteries and then summed to create a plaque score to represent the extent of atherosclerosis. Moderate carotid plaque was defined as the score ≥4 in whole carotid arteries.
Cranial MRI scanning protocol included sagittal T1-weighted localizer images and axial T1, proton density, and T2-weighted images. Axial T1-weighted, T2-weighted, and proton density-weighted scans were performed using a 1.5-T Siemens scanner, which uses continuous fluid-attenuated inversion recovery (repetition time, 6000 ms; echo time, 100 ms; inversion time, 2000 ms), and continuous turbo spin-echo T2-weighted sequence (repetition time, 2200 ms; echo time, 100 ms). In each scan, 19 transaxial slices (6.5-mm thickness) were obtained. The brain MRI images of the cortex, brain stem, and cerebellum were assessed to record potential ischemic lesions, including the absence or presence, number, and site. Two neurologists assessed the MRI images independently (inter-reader intraclass correlation = 0.90), blind to individual profiles. A consensus on inconsistent readings was reached through discussions by them. SBI was defined as a focal area ≥3 mm in diameter on T2-weighted images and continuous fluid-attenuated inversion recovery images.

**Definition and Identification**

Subjects with diagnosed diabetes mellitus were defined as subjects currently using hypoglycemic agents or 2 fasting plasma glucose levels ≥126 mg/dL in their medical records. Subjects with diagnosed hypertension were identified as subjects currently using antihypertensive medication or systolic BP/diastolic BP consistently at ≥140/90 mm Hg. eGFR was calculated with the modification of diet in renal disease formula with a 186 coefficient. For the purpose of attenuating the excessive influence on the results in analyses, those eGFR >150 ml/min/1.73 m² were regarded as 150 ml/min/1.73 m². We divided subjects according to their eGFR into groups 1, 2, 3a, and 3b, individually corresponding to eGFR levels of ≥90.0, 60.0 to 89.9, 45.0 to 59.9, and 30.0 to 44.9 ml/min/1.73 m². The grouping grossly corresponds to CKD staging according to the Kidney Disease Outcomes Quality Initiative guidelines.

**Statistical Analysis**

Continuous data were expressed as mean±SD, and categorical data were expressed as frequency and percentage. Baseline characteristics were compared among eGFR groups and examined by 1-way ANOVA and the trend test. The age-adjusted and sex-adjusted and multivariate logistic models were developed to estimate the risks (OR and 95% CI) of groups 2, 3a, and 3b compared with group 1 (the reference group). Because of the insufficient sample size of SBI, only the covariates with P<0.001 in univariate analysis were included in multivariate model. OR was also calculated and plotted by deducting the eGFR per 15 ml/min/1.73 m² and comparing it with that of 105 to 149.9 ml/min/1.73 m². A cubic spline model without knot was also used to explore the nonlinear influence of eGFR and SBI risk and is graphically presented in the Figure. Moreover, to determine the linear progressive trend of the eGFR to SBI risk, a logistic regression was performed with a continuous eGFR per SD after adjustments for the necessary covariates.

**Results**

Of these 1312 subjects (765 male and 547 female), mean age was 52.5±10.0 (range, 30–93) years, and mean eGFR was 93.8±20.2 (29.3–150.0) ml/min/1.73 m². For eGFR, 759 subjects were in group 1, 506 were in group 2, 31 were in group 3a, and 16 were in group 3b.

**Prevalence of SBI**

There were 62 subjects with SBI, and the crude prevalence was 4.7%. The prevalence of SBI in each eGFR group was 2.6% (20 of 759 subjects) in group 1, 6.3% (32 of 506) in group 2, 12.9% (4 of 31) in group 3a, and 37.5% (6 of 16) in group 3b. The increase in the presence of SBI was strongly related to a decrease in eGFR (P<0.001).

**Table 2. Characteristics of Participants With and Without Silent Brain Infarction**

<table>
<thead>
<tr>
<th></th>
<th>With Silent Brain Infarction</th>
<th>Without Silent Brain Infarction</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>62</td>
<td>1250</td>
<td></td>
</tr>
<tr>
<td>Male (%)</td>
<td>50 (80.7)</td>
<td>714 (57.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age 65 or older (%)</td>
<td>23 (37.1)</td>
<td>141 (11.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>28 (45.2)</td>
<td>246 (19.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>20 (32.3)</td>
<td>172 (13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Carotid plaque score ≥4 (%)</td>
<td>24 (38.7)</td>
<td>112 (9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of cardiovascular disease (%)</td>
<td>5 (8.1)</td>
<td>61 (4.9)</td>
<td>0.263</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>0 (0.0)</td>
<td>3 (0.24)</td>
<td>0.700</td>
</tr>
<tr>
<td>Past or current smoking habit (%)</td>
<td>29 (46.8)</td>
<td>463 (37.1)</td>
<td>0.126</td>
</tr>
<tr>
<td>Alcohol drinking habit (%)</td>
<td>18 (29.0)</td>
<td>367 (29.4)</td>
<td>0.953</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>138.5±21.3</td>
<td>122.3±20.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.5±12.9</td>
<td>73.5±11.6</td>
<td>0.019</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.8±3.5</td>
<td>24.6±3.3</td>
<td>0.012</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>213.3±43.6</td>
<td>207.1±36.8</td>
<td>0.276</td>
</tr>
<tr>
<td>Triglyceride, mg/dL</td>
<td>158.7±72.2</td>
<td>137.5±79.0</td>
<td>0.030</td>
</tr>
<tr>
<td>High-density lipoprotein, mg/dL</td>
<td>49.2±13.6</td>
<td>53.3±14.7</td>
<td>0.022</td>
</tr>
<tr>
<td>Low-density lipoprotein, mg/dL</td>
<td>124.9±34.5</td>
<td>121.0±30.3</td>
<td>0.388</td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein, mg/dL (%)</td>
<td>0.16 (0.28)</td>
<td>0.10 (0.19)</td>
<td>0.029</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>6.8±1.7</td>
<td>6.2±1.6</td>
<td>0.036</td>
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<tr>
<td>Hemoglobin, mg/dL</td>
<td>14.4±1.5</td>
<td>14.6±1.6</td>
<td>0.225</td>
</tr>
<tr>
<td>Albumin, mg/dL</td>
<td>4.50±0.25</td>
<td>4.55±0.27</td>
<td>0.264</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.04±0.36</td>
<td>0.85±0.21</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated glomerular filtration rate, ml/min/1.73 m²</td>
<td>81.7±24.1</td>
<td>94.5±19.8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The P values were from independent t test, median test, or χ² test. Data expressed by mean±SD, *median (interquartile range), or frequency (percent).

**Characteristics by eGFR Group**

Table 1 shows the demographic and clinical characteristics of all subjects grouped by eGFR. In general, the significant differences and significant trends in these eGFR groups were in age (65 years or older), gender, hypertension, diabetes, carotid plaque score (≥4), smoking habit, systolic BP and diastolic BP, body mass index, and levels of total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, high-sensitivity C-reactive protein, uric acid, hemoglobin and creatinine (all P<0.05).
Association Between the eGFR Groups and SBI

The presence of SBI was found to be related to age, gender, hypertension, diabetes, carotid plaque, systolic BP, diastolic BP, body mass index, and levels of triglyceride, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and uric acid (Table 2; all \( P < 0.05 \)). The age-adjusted and sex-adjusted effects for SBI risk in each eGFR group compared with that in group 1 did not increase except for group 3b (Table 3; model I, OR 11.91; 95% CI, 3.60–39.43; \( P < 0.001 \)). A similar significantly increasing risk in group 3b was seen (model II, OR, 10.56; 95% CI, 3.00–37.10; \( P < 0.001 \)) after adjusting for possible confounders.

The risk for SBI was 0.72 (95% CI, 0.54–0.96; \( P = 0.025 \)) per SD (20.2 mL/min/1.73 m\(^2\)) in increasing eGFR after adjusting for age, gender, hypertension, diabetes, and moderate carotid plaque, indicating that the SBI risk increases with decreasing eGFR. However, a significant increase in the presence of SBI appeared in the subjects with eGFR 30.0 to 44.9 mL/min/1.73 m\(^2\) (Figure). The Figure reveals a trend of progressive and incremental increases in OR when eGFR decreased per 15 mL/min/1.73 m\(^2\) from 105 mL/min/1.73 m\(^2\).

The cubic spline model expressed a nonlinear increase in OR when eGFR was 30.0 to 44.9 mL/min/1.73 m\(^2\) (Figure). The Figure reveals a trend of progressive and incremental increases in OR when eGFR decreased per 15 mL/min/1.73 m\(^2\) from 105 mL/min/1.73 m\(^2\). The results of our study further point out the high risk of prevalent SBI in CKD stage 3b (all OR \( \approx \times 10 \)).

Two possible explanations exist for the differences in SBI risk at these levels. First, our participants came from the general population, and the range in age was from 30 to 93 years. In contrast, the subjects in the study by Wada were aged 61 and 70 to 72, and the subjects in the study by Kobayashi were outpatients with CKD or essential hypertension. These differences would mask the actual risk effect of renal dysfunction that we wanted to discover.

Second, we selected subjects with an eGFR \( \geq 90 \) mL/min/1.73 m\(^2\) as the reference group, which was different from those in the studies by Wada and Kobayashi. They chose 60 mL/min/1.73 m\(^2\) as a cutoff point for the reference group. Our results revealed no significant risk effects for those eGFR groups \( \geq 45.0 \) mL/min/1.73 m\(^2\) but a critical risk for those with an eGFR 30.0 to 44.9 mL/min/1.73 m\(^2\). When we pooled groups 3a and 3b for multivariate analysis, the risk was still significant (OR, 3.80; 95% CI, 1.50–9.65) but somewhat underestimated.

Age, hypertension, diabetes, total cholesterol level, metabolic syndrome, and carotid atherosclerosis have been reported to be related to SBI risk.\(^{10–26}\) To extract the actual effect of CKD on SBI risk, we included age, gender, hypertension, diabetes, and carotid atherosclerosis in the multivariate model. We also compared the smoking habits, lipids profiles, obesity, and levels of uric acid, high-sensitivity C-reactive protein, hemoglobin, and albumin, but they are not significant. This allowed us to determine the critical risk present at stage 3b CKD.

SBI is a strong predictor of clinical overt stroke in general population,\(^{2–4}\) but in CKD the predictive effect needs more clinical studies to prove it. If so, then the high prevalence of SBI in a specific stage of CKD could forecast more frequent attacks of overt stroke beyond this stage. Unfortunately, our results cannot resolve this problem. We hope the finding of the high prevalence of SBI in specific CKD stages could arouse more attention for early detection of stroke in CKD.

An association between white matter lesion, a type of cerebral abnormality other than SBI, and eGFR or CKD has been reported in many studies.\(^{11,12,27,28}\) Of our 1312 subjects,
693 (52.8%) had white matter problems. Some dispute still exists on whether SBI or white matter lesion is the proper marker for cerebral vascular diseases in brain MRI images.\textsuperscript{12,13,29} However, the pathogenesis of SBI and white matter lesion is different. SBI represents a neuropathological change incorporating wall thickening and hyaline deposition in small end-perforating arterioles in the white matter of the brain.\textsuperscript{30} White matter lesion appears in neuronal loss, ischemic demyelination, and gliosis.\textsuperscript{31,32} White matter lesion can be present not only in stroke\textsuperscript{33} but also in multiple sclerosis and pyridoxine deficiency.\textsuperscript{34,35} Therefore, we consider SBI as the better marker for lacunar stroke in brain MRI images.

Even through an association of cardiovascular disease in CKD with abnormalities of large vessels, such as carotid change and arterial stiffness, was found\textsuperscript{36,37} the predictive ability of these abnormalities for cardiovascular disease development in CKD patients was questioned. Coll et al\textsuperscript{38} found in 2010 that the severity of carotid change and the ankle–brachial index could underestimate atherosclerosis in CKD. The progression of CKD largely involves the pathological change of small vessels.\textsuperscript{14,15} Some pathological changes in small vessels in early CKD, including glomeruli and small vessels in other organs, could develop early and not be predicted using traditional atherosclerotic risk factors. This is because all these factors are measured from the change of large, not small, vessels. This may explain the findings of a weak relationship between arterial stiffness and the eGFR in CKD in the Framingham Heart Study and the study by Sengstock,\textsuperscript{39,40} and the closer relationship found only in advanced CKD in the study by Ford.\textsuperscript{41} SBI is a disease of the small arteries, and SBI may be closer to CKD than large vessel disease in pathogenesis. Uzu et al\textsuperscript{42} found in 2010 that SBI predicted renal failure in type 2 diabetes. In our study, the presence of SBI is associated with the severity of renal dysfunction even after adjustment for carotid plaque.

The prevalence rates of SBI in the general population are from 5% in Korea to 30% in the United States.\textsuperscript{1,20,24,43,44} This difference partially results from the age of the people studied. In our study, the crude SBI prevalence is 4.7% in adults older than 30 years of age and 11.8% in those older than 60 years of age. This is similar to other studies in Asia. Moreover, the absence of advanced CKD in our study may be related to its rarity in the population that received self-paid physical examinations. Despite this, 47 subjects (3.6%) had the diagnosis of stage 3 CKD. This is close to the results (3.06%) for the general population found by Wen et al\textsuperscript{13} in Taiwan when the socioeconomic status of subjects studied is comparable. This shows that our population was representative of the general population in Taiwan. Some limitations should be discussed. First, because our subjects came from the general population, not all information on personal medication might have been given. Second, only 1 subject had stage 4 CKD and none had stage 5 in our original population. According to Wen,\textsuperscript{44} the prevalence of stages 4 and 5 CKD in Taiwan is only 0.06% and 0.04%, respectively. There is little difference in the percentages of CKD stages between the population used by Wen and our population.

**Conclusions**

We report the relationship between CKD stages 1 to 3 and the presence of SBI in adults from the general population. We have found the increase in the presence of SBI is strongly related to a decrease in eGFR, and a significant increase in the prevalence of SBI when eGFR is 30.0 to 49.9 mL/min/1.73 m\textsuperscript{2}. Adults with late stage 3 CKD are at high risk for prevalent SBI. It remains to be proven that early detection of SBI in late stage 3 CKD can minimize the threat of potential strokes.

**Sources of Funding**

The study was supported by grants from the National Science Council (NSC-98-2314-B341-005-MY2, NSC-97-2314-B341-004) and Shin Kong Wu Ho-Su Memorial Hospital (SKH-8302-95-DR-18, SKH-8302-99-NDR-07).

**Disclosures**

None.
References


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Stroke. published online June 23, 2011;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/early/2011/06/23/STROKEAHA.110.597930

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(Stroke. 2011;42:2120-2125.)

Key Words: chronic kidney disease ■ magnetic resonance imaging ■ silent brain infarction
Figure. Age-adjusted and sex-adjusted and multivariate-adjusted odds ratios (OR) for estimated glomerular filtration rate (eGFR) categories per 15 mL/min/1.73 m$^2$ (A) shown in broken line plot with 95% CI (B) shown in cubic spline plot. ***$P<0.001$. 

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**A**

- **Age & Sex adjusted**
- **Multivariate adjusted**

**B**

- **Age & Sex adjusted**
- **Multivariate adjusted**

**GFR categories**

**OR**

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[Graph images showing OR for different GFR categories with age and sex adjusted and multivariate adjusted models.]