Chronic Kidney Disease is a Risk Factor for Cardiovascular Death in a Community-Based Population in Japan

— NIPPON DATA90 —

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Background Chronic kidney disease (CKD) has been identified as a risk factor for cardiovascular disease (CVD).

Methods and Results The risk of cardiovascular death was evaluated in a large cohort of participants selected randomly from the overall Japanese population. Participants (mean age, 52.4 years) free of previous CVD were followed up for 10 years. Glomerular filtration rate (GFR) was estimated using the abbreviated equation developed at the Cleveland Clinic laboratory for the Modification of Diet in Renal Disease study. Of the 7,316 participants, 6.7% had CKD with a GFR <60 at baseline. Even after adjustment for other risk factors, the presence of CKD conferred an increased risk of cardiovascular death with a hazard ratio of 1.20 (95% confidence interval, 0.82–1.76). Furthermore, a negative, graded correlation between GFR and risk of cardiovascular death was observed: 1.09 (0.72–1.64) for a 60≤GFR<90, 1.15 (0.67–1.99) for a 45≤GFR<60, 1.23 (0.49–3.09) for a 30≤GFR<45, 5.52 (1.62–18.75) for a 15≤GFR<30, 9.12 (2.12–39.29) for a GFR<15, as compared with normal kidney function (GFR ≥90). The proportion of excess cardiovascular death due to CKD was 1.3%.

Conclusion CKD was an independent risk factor for cardiovascular death in a community-dwelling Japanese population. (Circ J 2006; 70: 954–959)

Key Words: Cardiovascular disease; Chronic kidney disease; Glomerular filtration rate; Mortality
Table 1  Baseline Risk Characteristics of 7,316 Participants in 1990 by Sex and Kidney Function Estimated by the Abbreviated MDRD Equation: NIPPON DATA90

<table>
<thead>
<tr>
<th>Age (years)*</th>
<th>GFR ≥90 (n=2,901)</th>
<th>GFR &lt;90 (n=146) p value</th>
<th>GFR ≥90 (n=3,924)</th>
<th>GFR &lt;90 (n=345)</th>
<th>p value</th>
<th>GFR ≥90 (n=2,901)</th>
<th>GFR &lt;90 (n=146) p value</th>
<th>GFR ≥90 (n=3,924)</th>
<th>GFR &lt;90 (n=345)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>GFR (ml/min per 1.73 m²)</td>
<td>52.6±13.3</td>
<td>67.3±11.3</td>
<td>&lt;0.01</td>
<td>50.6±13.1</td>
<td>68.9±11.1</td>
<td>&lt;0.01</td>
<td>50.6±13.1</td>
<td>68.9±11.1</td>
<td>&lt;0.01</td>
<td>50.6±13.1</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl)*</td>
<td>85.5±15.4</td>
<td>51.4±9.7</td>
<td>&lt;0.01</td>
<td>87.3±16.8</td>
<td>52.5±8.9</td>
<td>&lt;0.01</td>
<td>87.3±16.8</td>
<td>52.5±8.9</td>
<td>&lt;0.01</td>
<td>87.3±16.8</td>
</tr>
<tr>
<td>Body mass index (kg/m²)*</td>
<td>23.1±3.0</td>
<td>21.5±1.7</td>
<td>0.11</td>
<td>22.8±3.3</td>
<td>23.5±3.2</td>
<td>&lt;0.01</td>
<td>22.8±3.3</td>
<td>23.5±3.2</td>
<td>&lt;0.01</td>
<td>22.8±3.3</td>
</tr>
<tr>
<td>Smoking habit†</td>
<td>Never smoked (%)</td>
<td>21.1</td>
<td>15.1</td>
<td>0.01</td>
<td>88.5</td>
<td>88.7</td>
<td>0.01</td>
<td>88.5</td>
<td>88.7</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Ex-smoker (%)</td>
<td>22.5</td>
<td>37.0</td>
<td>&lt;0.01</td>
<td>2.4</td>
<td>4.1</td>
<td>&lt;0.01</td>
<td>2.4</td>
<td>4.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Current smoker (%)</td>
<td>56.4</td>
<td>47.9</td>
<td>&lt;0.01</td>
<td>9.1</td>
<td>7.2</td>
<td>0.01</td>
<td>9.1</td>
<td>7.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Drinking habit†</td>
<td>Never drank (%)</td>
<td>34.5</td>
<td>45.2</td>
<td>&lt;0.01</td>
<td>92.2</td>
<td>97.4</td>
<td>&lt;0.01</td>
<td>92.2</td>
<td>97.4</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Ex-drinker (%)</td>
<td>5.7</td>
<td>12.3</td>
<td>&lt;0.01</td>
<td>1.0</td>
<td>0.0</td>
<td>&lt;0.01</td>
<td>1.0</td>
<td>0.0</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td></td>
<td>Daily drinker (%)</td>
<td>59.7</td>
<td>42.5</td>
<td>&lt;0.01</td>
<td>6.8</td>
<td>2.6</td>
<td>&lt;0.01</td>
<td>6.8</td>
<td>2.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension (%)†</td>
<td>48.2</td>
<td>71.9</td>
<td>&lt;0.01</td>
<td>39.3</td>
<td>72.8</td>
<td>&lt;0.01</td>
<td>39.3</td>
<td>72.8</td>
<td>&lt;0.01</td>
<td>39.3</td>
</tr>
<tr>
<td>Diabetes mellitus (%)†</td>
<td>7.0</td>
<td>15.1</td>
<td>&lt;0.01</td>
<td>3.7</td>
<td>8.1</td>
<td>&lt;0.01</td>
<td>3.7</td>
<td>8.1</td>
<td>&lt;0.01</td>
<td>3.7</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)†</td>
<td>16.4</td>
<td>24.7</td>
<td>&lt;0.01</td>
<td>21.3</td>
<td>38.0</td>
<td>&lt;0.01</td>
<td>21.3</td>
<td>38.0</td>
<td>&lt;0.01</td>
<td>21.3</td>
</tr>
<tr>
<td>Left high voltage on ECG (%)</td>
<td>17.0</td>
<td>18.5</td>
<td>0.05</td>
<td>5.9</td>
<td>8.1</td>
<td>0.10</td>
<td>5.9</td>
<td>8.1</td>
<td>0.10</td>
<td>5.9</td>
</tr>
</tbody>
</table>

Values are mean±SD or the % of participants in that category.

*One-way analysis of variance.
†Chi-square test.

GFR, glomerular filtration rate; ECG, electrocardiogram.

Statistics were coded according to the 9th International Classification of Disease for deaths occurring to the end of 1994 and the 10th International Classification of Disease for deaths occurring from the beginning of 1995. The details of death classification in the present study are described elsewhere.13–16

We were permitted to use the National Vital Statistics by the CDC-NHLBI (Centers for Disease Control/National Heart, Lung, and Blood Institute) Lipids Standardization program.22 Hypercholesterolemia was defined as serum total cholesterol ≥240 mg/dl, medication for hypercholesterolemia or both. Plasma glucose (mg/dl) was also measured using an enzymatic method. Diabetes mellitus was defined as plasma glucose ≥200 mg/dl, medication for diabetes mellitus or both.

A standard 12-lead electrocardiogram (ECG) was recorded in the supine position. Each record was coded independently by 2 researchers according to the Minnesota Code.23 Codes in agreement were accepted, whereas codes in disagreement were adjudicated by a panel of study epidemiologists and cardiologists. Left high R-wave was defined as R-wave in V5 or V6 ≥2.6 mV, or R-wave in I, II, III or aVF ≥2.0 mV, or R-wave in aV1 ≥1.2 mV (the Minnesota Code, 3-1), and/or R-wave in V1 ≥1.5 mV but ≥2.0 mV, or S-wave in V1 plus R-wave in V5 or V6 >3.5 mV (the Minnesota Code, 3-3).

Baseline blood pressure was measured by trained observers using a standard mercury sphygmomanometer on the right arm of seated participants after a sufficient period of rest. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, medication for hypertension, or any combination of these.

Body mass index (BMI) was calculated using the following equation: [weight (kg)/height (m)²]. Public health nurses obtained information on smoking, drinking, and medical histories.
There were 70,006 person-years of follow-up for the 7,316 participants (mean age, 52.4 years) in the study. Among all the participants, 655 died, including 74 who died from strokes and 101 who died from heart disease. The mean value of GFR calculated using the abbreviated MDRD equation and the Cockcroft-Gault equation in all the participants was 84.2 and 92.1 ml/min per 1.73 m², respectively.

The baseline risk characteristics of participants classified into 2 groups based on GFR calculated using the abbreviated MDRD equation are summarized in Table 1. Of all the participants, 6.7% had CKD with GFR <60 at baseline. The mean value of age and the prevalence of hypertension, diabetes mellitus, hypercholesterolemia and left high voltage on ECG were higher in the participants with CKD, whereas the mean value of BMI for women was higher in the participants with CKD. In addition, the prevalence of current smokers, daily drinkers, diabetes mellitus and left high voltage on the ECG was higher in men than women in all categories of kidney function.

Of all the participants, 8.5% had CKD at baseline, evaluated using the Cockcroft-Gault equation. The baseline risk characteristics of participants classified into 2 groups based on GFR calculated using the Cockcroft-Gault equation were similar to the results presented in Table 1 (data not shown).

When we performed sex-specific analyses of the relationships between death and CKD based on GFR calculated...
using the abbreviated MDRD equation and the Cockcroft-Gault equation, the results were similar for men and women. Therefore, we analyzed and reported the relationships for both sexes combined.

The participants with CKD based on GFR calculated using the abbreviated MDRD equation had a multivariate-adjusted hazard ratio of 1.31 (95% confidence interval (CI), 1.06 to 1.60) for all-cause death, 1.20 (95% CI, 0.82 to 1.76) for cardiovascular death, 0.62 (95% CI, 0.31 to 1.22) for stroke death, 1.65 (95% CI, 1.01 to 2.72) for heart disease death, compared with the participants without CKD. The participants with more severe kidney dysfunction tended to have a higher multivariate-adjusted hazard ratio for all-cause and cardiovascular death (Table 2). The proportion of excess cardiovascular death due to CKD was 1.3%, when using a prevalence of 6.7% and a hazard ratio of 1.20.

The participants with CKD based on GFR calculated using the Cockcroft-Gault equation had a multivariate-adjusted hazard ratio of 1.47 (95% CI, 1.21 to 1.80) for all-cause death, 1.51 (95% CI, 1.04 to 2.20) for cardiovascular death, 0.98 (95% CI, 0.54 to 1.76) for stroke death, 2.20 (95% CI, 1.32 to 3.69) for heart disease death, compared with the participants without CKD. The participants with more severe kidney dysfunction tended to have a higher multivariate-adjusted hazard ratio for all-cause and cardiovascular death (Table 3). The proportion of excess cardiovascular death due to CKD was 4.2%, when using a prevalence of 8.5% and a hazard ratio of 1.51.

**Discussion**

In the present prospective, community-based study, CKD defined as a GFR less than 60 ml/min per 1.73 m² was an independent risk factor for cardiovascular death. Depending on the equation used to calculate GFR, the prevalence of CKD was 6.7–8.5% in the present study population. CKD contributed to excess cardiovascular death by 1.3–4.2%.

CKD represents a reduction of the normal GFR level in young individuals by more than half. This condition was found by the prevalence of 6.7–8.5% in the present study population. Two previous studies in a community-based population in Japan also reported a prevalence of CKD of approximately 10% or less. Therefore, the prevalence of CKD may be approximately 10% in the community-dwelling population in Japan in general.

CKD is associated with increased prevalence and severity of traditional cardiovascular risk factors such as hypertension. Increased levels of traditional cardiovascular risk factors may have an effect on CVD. Furthermore, traditional cardiovascular risk factors are associated with a decline in renal function. Thus, CKD may be a marker for CVD, which includes the effects of traditional cardiovascular risk factors. However, the risk of CKD for CVD is independent of traditional cardiovascular risk factors, which was confirmed in the present study. Increased non-traditional cardiovascular risk factors related to CKD, such as hyper-
homocysteinemia\textsuperscript{25,26} may also be associated with CVD. However, we could not adjust our statistical analysis for such risk factors because they were not measured. In addition to the effects of cardiovascular risk factors on renal function, CKD itself may decrease cardiac function\textsuperscript{27}.

Furthermore, we demonstrated a negative, graded correlation between GFR and the risk of cardiovascular death. However, the relationship between GFR and risk depended on the equation used to calculate GFR. Using the abbreviated MDRD equation to calculate GFR, the risk of cardiovascular death tended to increase at a GFR <60, compared with normal kidney function (GFR >90). In contrast, when GFR was calculated using the Cockcroft-Gault equation, the risk tended to increase at a GFR <60. We should be careful in interpreting these results because of the limited number of participants who died from CVD in the groups with a lower GFR. Irie et al reported that the risk of cardiovascular death due to kidney dysfunction, when calculated using the abbreviated MDRD equation (but without correcting the GFR for Japanese), tended to increase at a GFR <70 in men and a GFR <60 in women, compared with normal kidney function (GFR >100).\textsuperscript{3} However, that study did not evaluate the risk of cardiovascular death due to more severe kidney dysfunction. If we take the correction of GFR into account in the present study, our results are consistent with those of Irie et al. When we calculate GFR using the abbreviated MDRD equation, it may be appropriate to regard a GFR of 60 ml/min per 1.73 m\textsuperscript{2} as the cutoff value for increasing the risk of cardiovascular death in Japanese. On the other hand, we would predict more excess cardiovascular death due to CKD, when GFR is calculated using the Cockcroft-Gault equation. However, there are some controversies as to whether the MDRD and Cockcroft-Gault equations are applicable to Japanese. Therefore, further investigations of the influence of CKD on the risk of CVD in the Japanese population are needed.

Study Limitations

First, GFR was estimated using 2 simplified prediction equations. Furthermore, when we used the abbreviated MDRD equation to calculate GFR, which includes a term based on race (black and white),\textsuperscript{17,18} we regarded Japanese as white. Second, the classification of our participants was based only on the baseline GFR. Changes in GFR during the 10-year follow-up period were not taken into account. Finally, the details of medication status were not available based only on the baseline GFR. Changes in GFR during the 10-year follow-up period were not taken into account.

In conclusion, kidney dysfunction may be an important risk factor for cardiovascular death in Japanese. Appropriate strategies are needed for identifying and intervening in high-risk individuals with kidney dysfunction.\textsuperscript{29,30}

Acknowledgements

This study was supported by a Grant-in-Aid from the Ministry of Health and Welfare under the auspices of the Japanese Association for Cerebrocardiovascular Disease Control, a Research Grant for Cardiovascular Diseases (7A-2) from the Ministry of Health, Labour and Welfare and a Health and Labour Sciences Research Grant, Japan (Comprehensive Research on Aging and Health: H11-chouju-046, H14-chouju-003, H17-chouju-012).

References


Appendix 1

NIPPON DATA90 Research Group

NIPPON DATA90: National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged.

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