Relationship Between Blood Pressure Category and Incidence of Stroke and Myocardial Infarction in an Urban Japanese Population With and Without Chronic Kidney Disease

The Suita Study

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Background and Purpose—Chronic kidney disease (CKD) is increasingly recognized as an independent risk factor for stroke and myocardial infarction (MI). Few studies, however, have examined the relationship between blood pressure (BP) category and these diseases in subjects with and without CKD.

Methods—We studied 5494 Japanese individuals (ages 30 to 79, without stroke or MI at baseline) who completed a baseline survey and received follow-up through December 2005. The glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease study equation modified by the Japanese coefficient. CKD was defined as an estimated GFR <60 mL/min/1.73m². BP categories were defined by the European Society of Hypertension and European Society of Cardiology 2007 criteria.

Results—In 64 395 person-years of follow-up, we documented 346 incidences of cardiovascular diseases (CVD; 213 strokes and 133 MI events). Compared with the GFR (≥90 mL/min/1.73m²) group, the hazard ratios (95% confidential intervals) for stroke were 1.9 (1.3 to 3.0) in the GFR 50 to 59 mL/min/1.73m² group and 2.2 (1.2 to 4.1) in the GFR <50 mL/min/1.73m² group. Results for cerebral infarction were similar. Compared with the optimal BP subjects without CKD, the normal BP, high-normal BP, and hypertensive subjects without CKD showed increased risks of CVD and stroke; however the impact of each BP category on CVD (P for interaction: 0.04 in men, 0.49 in women) and stroke (0.03 in men, 0.90 in women) was more evident in men with CKD.

Conclusions—CKD may increase the association of BP and CVD in a Japanese urban population. (Stroke. 2009;40:2674-2679.)

Key Words: chronic kidney disease ▪ blood pressure category ▪ stroke ▪ myocardial infarction ▪ epidemiology ▪ prospective studies ▪ general population

Recently, chronic kidney disease (CKD) has become a major public health problem and a risk factor for all-causes mortality, stroke, and myocardial infarction (MI). In end-stage renal disease, the cardiovascular disease (CVD) mortality rate is more than 10 times as high as that in the general population. In asymptomatic general populations or outpatients, a severely or moderately decreased glomerular filtration rate (GFR) has been shown by most but not all studies to be an independent risk factor for stroke and MI. However, in low-risk or general populations, the relationship between levels of kidney function and clinical outcomes has not been as clear. Some studies have demonstrated no association between CKD and CVD, whereas others have shown CKD as an independent risk factor for CVD. These inconsistencies may be attributable to differences between the selected study populations as well as the severity of the CKD.

The frequency of hypertension is relatively higher in Japanese than in Western countries. Hypertension is one of the major risk factors for both CVD and CKD. Recently, a larger prospective study has indicated that CKD increased the association between blood pressure (BP) categories and CVD, although the relevant data were gathered from 10 rural areas with different methods.
for the measurement of creatinine. A few studies in general population have demonstrated a stronger association between BP and CVD in subjects with CKD. We examined the association between BP category and incidence of stroke and MI subjects with and without CKD in a Japanese urban population.

Methods

Study Subjects

Suita city is located adjacent to Osaka city, which is the second largest metropolitan area in Japan. The Suita Study, an epidemiological study of cerebrovascular and cardiovascular diseases, was based on a random sampling of 12 200 Japanese urban residents. As a baseline, participants (aged 30 to 79 years) were randomly selected from the municipality population registry and stratified into groups by sex and age in 10-year increments in 1989. Of these, 6485 people underwent regular health checkups between September 1989 and March 1994.

Cohort members in the study population were excluded from these analyses if they had a past or present history of CVD at baseline (n = 208), were missing data (n = 170), attended health checkups after April 1994 (n = 79), or failed to complete the follow-up health surveys or questionnaires after the baseline examination (n = 534). After applying these exclusions, a total of 5494 participants aged 30 to 79 years old were selected. Informed consent was obtained from all participants. This study was approved by the Institutional Review Board of the National Cardiovascular Center.

Measurement of Blood Pressure and Covariates

Well-trained physicians measured BP 3 times using a mercury column sphygmomanometer, an appropriate-size cuff, and a standard protocol. Before the initial BP reading was obtained, participants were seated at rest for at least 5 minutes. First, systolic blood pressure (SBP) was measured for the purpose of obtaining approximate SBP levels. SBP and diastolic blood pressures (DBP) were taken as the average of the second and third measurements, which were recorded more than 1 minute apart.

At the time of the baseline examination, subjects were classified into 1 of the 5 BP categories based on the European Society of Hypertension and European Society of Cardiology (ESH-ESC) 2007 criteria: optimal (SBP <120 mm Hg and DBP <80 mm Hg), normal (SBP 120 to 129 mm Hg or DBP 80 to 84 mm Hg), high-normal BP (SBP 130 to 139 mm Hg or DBP 85 to 89 mm Hg), and hypertensive (SBP ≥140 mm Hg or DBP ≥90 mm Hg). Antihypertensive drug users were classified according to their BP levels at the baseline examination. If the SBP and DBP readings for a subject were in different categories, the subjects were categorized into the higher of the two BP categories.

At the baseline examination, we performed routine blood tests that included serum total cholesterol, HDL cholesterol, and glucose levels. Physicians or nurses administered questionnaires covering personal habits and present illness. Body mass index (BMI) was calculated as weight (kilograms) divided by height (meters) squared. Hypercholesterolemia was defined as total cholesterol levels ≥5.7 mmol/L or current use of antihyperlipidemic medications. Diabetes was defined as a fasting plasma glucose level ≥7.0 mmol/L, a nonfasting plasma glucose level ≥11.0 mmol/L, or current use of antidiabetic medications.

Definition of CKD

Serum creatinine (Cre) was measured by uncompensated kinetic Jaffé methods. The glomerular filtration rate (GFR) of each participant was calculated from the Cre value and the age, using the MDRD equation modified by the Japanese coefficient (0.881), as follows:

\[
GFR (\text{ml/min/1.73 m}^2) = 0.881 \times 186 \times \text{age}^{-0.203} \times \text{Cre}^{-1.154} \quad \text{(for men)}
\]

and

\[
GFR (\text{ml/min/1.73 m}^2) = 0.881 \times 186 \times \text{age}^{-0.203} \times \text{Cre}^{-1.212} \times 0.742 \quad \text{(for women)}.
\]

CKD was defined as an estimated GFR <60 mL/min/1.73 m².

Confirmation of Stroke and MI and End Point Determination

The confirmation of stroke and MI in the Suita Study has been described elsewhere. In brief, the 5 hospitals in this area, where acute stroke and MI patients were admitted, were all capable of performing computed tomographic scans or MRI. Medical records were reviewed by registered hospital physicians or research physicians who were blinded to the baseline data. Strokes were defined according to the U.S. National Survey of Stroke criteria. For each stroke subtype (ie, cerebral infarction [thrombotic or embolic infarction], intracerebral hemorrhage, and subarachnoid hemorrhage), a definite diagnosis was established based on examination of computed tomographic scans, magnetic resonance images, or autopsies. Definite and probable MIs were defined according to the criteria set out by the MONICA project. Sudden deaths of unknown origin were deaths that occurred within 24 hours from the onset of symptoms, and were also classified as MI. In this study CVD was defined as stroke or MI.

To detect MI and stroke occurrences, each participant’s health status was checked at clinical visits to the National Cardiovascular Center every 2 years. Yearly questionnaires by mail or telephone were also completed for all participants. In addition, to complete our surveillance for fatal strokes and MIs, we conducted a systematic search for death certificates. All the data (health check-ups, questionnaires, and death certificates) were checked against medical records to confirm the incidence of CVD. We identified possible strokes or MIs using data from (1) the health examination and questionnaires from the stroke and MI registries without informed consent for medical records survey; and (2) death certificates bearing a diagnosis of probable stroke or MI without registration of CVD incidence.

The end points of the current follow-up study were (1) date of the first MI or stroke event; (2) date of death; (3) date of leaving Suita; and (4) December 31, 2005 (censored).

Statistical Analysis

Analyses of variances and χ² tests were used to compare mean values and frequencies. The Cox proportional-hazard ratios (HRs) were fitted to the GFR categories and CKD after adjusting for sex and age in 5-year increments as stratified variables and other potential confounding factors at the baseline survey: namely, present illness of hypertension, hypercholesterolemia and diabetes, smoking status (never, quit, and current smoker), and drinking status (never, quit, and current drinker). The Cox proportional HRs were fitted to the combination of the BP categories and CKD (positive or negative) after adjusting for sex and age in 5-year increments as stratified variables and other potential confounding factors including an interactive term for CKD and BP categories. The fit of the proportional hazards model was evaluated by examining discrete regression models and by permitting the proportionality assumption to vary with time, and assessments of nonlinearity involving associations with blood pressure and GFR categories were made. The probability values for the model of interaction between CVD incidence and log (person year) were 0.38 in men and 0.81 in women. Proportionality was also checked by log-log survival plot.

To express the impact of CKD on CVD occurrence in the participants, we estimated the population attributable fraction (PAF, %). PAF was estimated as follows:

\[ P_e \times (HR – 1)/HR, \]

in which Pe is the proportion of incident cases in CKD, and HR is the multiple-adjusted hazard ratio. All statistical analyses were conducted using the SAS statistical package software (release version 8.2, SAS Institute Inc).

Results

Figure 1 shows that the frequency of CKD increases with age in both men and women. At the baseline survey, both men and women with CKD (8.9% for men and 11.3% for women)
were older, had higher prevalence of hypertension and hypercholesterolemia, and had a lower frequency of current drinking than those without CKD (Table 1).

During an average 11.7-year follow-up period, we documented 213 strokes and 133 MIs. In men and women combined, compared with subjects for GFR $\geq 90$ mL/min/1.73m$^2$ the multivariable HRs (95% confidence intervals; CIs) for CVD incidence were 1.75 (1.22 to 2.50) in GFR $50$ to $59$ mL/min/1.73m$^2$ and 2.48 (1.56 to 3.94) in $<50$ mL/min/1.73m$^2$ (Table 2). In addition, the risks of CVD for each GFR category in men and women separately were similar to the risks for all participants. The multivariable HR (95% CIs) of CVD incidence for CKD was 1.70 (1.30 to 2.23) in all subjects (data not shown).

In Table 3, the multivariable HRs (95% CIs) for strokes were 1.94 (1.26 to 2.98) in the GFR $=50$ to $59$ mL/min/1.73m$^2$ and 2.19 (1.18 to 4.06) in the GFR $<50$ mL/min/1.73m$^2$ compared with subjects for GFR $\geq 90$ mL/min/1.73m$^2$ Results for cerebral infarction were similar to strokes. Age-adjusted HRs (95% CIs) for intracerebral hemorrhage were 1.93 (0.77 to 4.85) in the GFR $=50$ to $59$ mL/min/1.73m$^2$ and 2.52 (0.72 to 8.80) in the GFR $<50$ mL/min/1.73m$^2$ (supplemental Table I, available online at http://stroke.ahajournals.org).

In Figure 2, compared with the optimal BP subjects without CKD, the normal BP, high-normal BP, and hypertensive subjects without CKD showed increased risks of CVD, whereas the impact of each BP category on CVD was more evident in subjects with CKD (probability values for interaction between CKD and BP category were 0.04 in men, 0.49 in women, and 0.06 in all subjects). Results of stroke were similar (probability values for the interaction were 0.03 in men and 0.90 in women, data not shown). Supplemental Table II shows the hazard ratios for the association between 10 mm Hg of SBP and the risk of CVD in subjects with or without CKD.

Using the HRs, we estimated the population attributable fraction of CVD to exposure for CKD at baseline by sex. We found that 8.3% in men and 17.6% in men with CVD incidences could be described as excessive incidence attributable to CKD.

### Discussion

In this cohort study of a general urban Japanese population, CKD was a risk factor for CVD and its subtypes. A stronger association between BP and the incidence of CVD was
observed in the presence of CKD. Furthermore, we found that 8% in men and 18% in women of CVD incidence may be derived from CKD cases.

Go et al reported that both severe and moderate renal diseases were risk factors for CVD incidence. A pooled analysis of community-based studies demonstrated that CKD is an independent risk factor for the composite of all-cause mortality in blacks and whites and CVD incidence in blacks. In contrast, NHANES I did not provide relationships between mortality and moderately higher serum creatinine levels. The Framingham Heart Study and Offspring cohorts have shown no significant association between the presence of kidney disease and CVD incidence.

The results of our study are essentially compatible with previous cohort studies in Japan. The Hisayama study demonstrated that CKD was a risk factor for incidence of coronary heart disease in men and ischemic stroke in women. The Ohasama study indicated that decreased kidney function increased the risk of first symptomatic stroke events. This study used creatinine clearance rather than estimated GFR. Irie et al showed that subjects with GFR >60 had a higher risk of CVD mortality but did not examine the risk of GFR 50 to 59 mL/min/1.73m². The NIPPON DATA 90 indicated that CKD was an independent risk factor for cardiovascular death in a community-dwelling Japanese population. The end point of these studies was also mortality. Ninomiya et al reported that both severe and moderate renal diseases were risk factors for CVD incidence.

### Table 2. Age and Multivariable Adjusted Hazard Ratios (95% CIs) for Incidence of Cardiovascular Disease† According to Category of Glomerular Filtration Rate by Sex

<table>
<thead>
<tr>
<th>Variables</th>
<th>Glomerular Filtration Rate, ml/min/1.73m²</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥90</td>
<td>60 to 89</td>
</tr>
<tr>
<td>Men and Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>28 736</td>
<td>29 336</td>
</tr>
<tr>
<td>Person-years</td>
<td>1 2.02 (0.94–1.58)</td>
<td>1.71 (1.20–2.42)</td>
</tr>
<tr>
<td>Multivariable adjusted*</td>
<td>1.21 (0.93–1.58)</td>
<td>1.75 (1.22–2.50)</td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>50</td>
<td>124</td>
</tr>
<tr>
<td>Person-years</td>
<td>12 092</td>
<td>14 835</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1 1.20 (0.85–1.70)</td>
<td>1.63 (1.00–2.68)</td>
</tr>
<tr>
<td>Multivariable adjusted*</td>
<td>1 1.21 (0.85–1.70)</td>
<td>1.78 (1.08–2.94)</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>44</td>
<td>52</td>
</tr>
<tr>
<td>Person-years</td>
<td>16 644</td>
<td>14 502</td>
</tr>
<tr>
<td>Age-adjusted</td>
<td>1 1.22 (0.81–1.83)</td>
<td>1.79 (1.09–2.92)</td>
</tr>
<tr>
<td>Multivariable adjusted*</td>
<td>1 1.21 (0.80–1.84)</td>
<td>1.76 (1.05–2.93)</td>
</tr>
</tbody>
</table>

*Multivariable adjusted for age, BMI, smoking, drinking, and present illness (hypertension, diabetes, and hypercholesterolemia).
†Cardiovascular disease includes both stroke and MI.

### Table 3. Age-Sex and Multivariable Adjusted Hazard Ratios (95% CIs) for Incidence of All Strokes, Cerebral Infarction, and Myocardial infarction According to Category of Glomerular Filtration Rate

<table>
<thead>
<tr>
<th>Variables</th>
<th>Glomerular Filtration Rate, ml/min/1.73m²</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥90</td>
<td>60 to 89</td>
</tr>
<tr>
<td>Person-years</td>
<td>28 258</td>
<td>28 690</td>
</tr>
<tr>
<td>All strokes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>65</td>
<td>99</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1 1.02 (0.73–1.41)</td>
<td>1.78 (1.17–2.70)</td>
</tr>
<tr>
<td>Multivariable adjusted*</td>
<td>1 1.04 (0.74–1.45)</td>
<td>1.94 (1.26–2.98)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>42</td>
<td>66</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1 0.99 (0.66–1.49)</td>
<td>1.72 (1.03–4.19)</td>
</tr>
<tr>
<td>Multivariable adjusted*</td>
<td>1 0.98 (0.65–1.49)</td>
<td>1.81 (1.07–3.07)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases, n</td>
<td>29</td>
<td>77</td>
</tr>
<tr>
<td>Age and sex adjusted</td>
<td>1 1.68 (1.08–2.61)</td>
<td>1.64 (0.87–3.09)</td>
</tr>
<tr>
<td>Multivariable adjusted*</td>
<td>1 1.60 (1.03–2.49)</td>
<td>1.51 (0.80–2.88)</td>
</tr>
</tbody>
</table>

*Multivariable adjusted for age, sex, BMI, smoking, drinking, and present illness (hypertension, diabetes, and hypercholesterolemia).
has recently reported that CKD was risk factors for CVD and stroke in women and that CKD increased the association between BP category and CVD in all subjects from 10 combined different cohort studies using different methods of creatinine measurement. All of our samples were measured using the same analyzer at one laboratory.

Compared with the previous studies, our study has several methodological strengths. First, we could perform subanalysis by age and CVD subtype, because we evaluated a large cohort of participants. Second, each participant’s health status was checked during a clinical visit at the National Cardiovascular Center every 2 years. In addition, each year, a health questionnaire was given to each participant via mail or telephone. We could evaluate the registry of CVD incidence with the data obtained from clinical visits, annual questionnaires, or death certificates. Finally, our cohort population was selected at random from an urban population, in contrast to most other cohort studies in Japan, which have relied on rural populations.

There may be some reasons why CKD is more positively associated with CVD in blacks or Japanese than in whites. Blacks and Japanese are more likely to have hypertension at an earlier age. Therefore, the period of hypertension exposure tends to be longer in blacks and Japanese than in whites. The GFR estimation has been adjusted by a factor suitable for Japanese populations.

Reduced kidney function is associated with increased levels of inflammatory factors, abnormal apolipoprotein levels, elevated plasma homocysteine, enhanced coagulability, anemia, left ventricular hypertrophy, increased arterial calcification, endothelial dysfunction, and arterial stiffness. How these and other factors interact to increase the risk of adverse outcomes remains unclear but is the focus of ongoing investigations.

Subjects with GFR levels of 50 to 59 mL/min/1.73m² were observed to be at risk for stroke. It is desirable to prevent CVD in subjects with both high-risk (<50 mL/min/1.73m²) and less severe kidney disease (50 to 59 mL/min/1.73m²), although an accelerated decline in GFR occurred for the subjects whose initial GFR <50 mL/min/1.73m².

Hypertension is a strong risk factor for early decline in kidney function; hypertensive patients (BP ≥160/95 mm Hg) have a 5-fold greater decline in GFR (2.7 mL/min/1.73m²/yr) compared with patients with BP <140/90 mm Hg. Furthermore, in this study, the association between BP and the incidence of CVD were evident by CKD. The risk of CVD was higher in CKD subjects with normal and high-normal BP than in non-CKD subjects in the same BP categories. Using the combination of BP and CKD, it could be possible to screen more efficiently for higher risk of stroke and MI. This is compatible with the CKD clinical guidelines, which state that the preferable BP for subjects with CKD is 130/80 mm Hg. For the prevention of CVD incidence for all hypertensive subjects in health check-ups, it might be desirable to measure serum creatinine levels and to intervene in lifestyle modification such as reducing salt intake, more frequent exercise, or quit smoking.

Our study has several limitations. The primary limitation is dilution bias, in that the current study was based on single-day measurement of creatinine levels. The creatinine levels might have been misclassified, despite the fact that measurements of creatinine levels on a single day have been found to be accurate in other epidemiological studies. Second, we did not perform a creatinine clearance test or 2 measurements of serum creatinine at least 3 months apart. Although our definition of CKD is based on a single assessment of serum creatinine, the equation provides an accurate estimated GFR value. Third, even with the moderate sample size (n=5494) and 12-year duration, the numbers of end points were limited, especially when the data were stratified by 2 variables, such as sex and glomerular filtration rates. A study with more participants with the same protocol is required to validate to the association between BP category and CVD by CKD.

In conclusion, CKD was associated with an increased risk for stroke and MI in a general urban Japanese population. Furthermore, the association between BP and CVD may be evident by CKD. To prevent the incidence of stroke and MI, it is necessary for subjects with CKD to control their BP by lifestyle modification and proper clinical treatment.
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Disclosures
None.

References


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