Trends for Blood Pressure and Its Contribution to Stroke Incidence in the Middle-Aged Japanese Population

The Circulatory Risk in Communities Study (CIRCS)

Hironori Imano, MD; Akihiko Kitamura, MD; Shinichi Sato, MD; Masahiko Kiyama, MD; Tetsuya Ohira, MD; Kazumasu Yamagishi, MD; Hiroyuki Noda, MD; Takeshi Tanigawa, MD; Hiroyasu Iso, MD; Takashi Shimamoto, MD

Background and Purpose—Hypertension is a major risk factor for stroke. However, a substantial decrease in blood pressure levels in Japanese during the past 3 decades may have reduced contributions of hypertension to risk of stroke. The population attributable fraction, the percentage of outcomes attributable to exposure, of blood pressure for the incidence of stroke was investigated during 3 survey periods between 1963 and 1994 by means of a population-based cohort study.

Methods—We explored 3 cohort data of residents aged 40 to 69 years in 4 Japanese communities in 1963 to 1971 (n=5439), 1975 to 1984 (n=9945), and 1985 to 1994 (n=11788) baseline surveys. Mean follow-up period for each cohort was 10 years.

Results—Higher blood pressure levels were associated with higher risk of stroke. Positive associations were also observed even within nonhypertension levels. From the first to the third cohorts, the blood pressure category with a majority of stroke incidence shifted from severe or moderate hypertension to mild hypertension. The population attributable fraction of the severe hypertension category in the first, second, and third cohorts were 20%, 14%, and 9%, respectively, and those of the moderate hypertension category were 19%, 24%, and 11%, respectively, whereas those of the mild hypertension category were 17%, 26%, and 23%, respectively. The results were similar when participants on antihypertensive medication were excluded.

Conclusions—The higher risk of stroke incidence with higher blood pressure levels even in nonhypertension categories and the shift of stroke burden from severe/moderate hypertension to mild hypertension support the early management of hypertension and primary prevention of high blood pressures for the prevention of stroke. (Stroke. 2009;40:1571-1577.)

Key Words: blood pressure ■ population attributable fraction ■ stroke ■ incidence ■ follow-up study
of blood pressure categories for risk of stroke incidence using 3 10-year cohorts from the 1960s, 1970s, and 1980s. Those cohort investigations were performed by the same institute and unified protocols.

The original purpose of our study is to investigate risk factors, cardiovascular disease incidence, and their trends in Japanese communities, namely the Circulatory Risk in Communities Study (CIRCS).

Subjects and Methods

Study Populations

The study populations were residents aged 40 to 69 years of 4 communities: (1) Ikawa town,7,11 Akita Prefecture (a northeastern rural community); (2) Minami-Takayasu district,7 Yao City, Osaka Prefecture (a southwestern suburb); (3) Nochi town,12 Kochi Prefecture (a southwestern rural community); and (4) Kyowa town,13 Ibaraki Prefecture (a central rural community). We constructed 3 cohorts, ie, the first cohort: (1) 1963 to 1966; (2) 1966 to 1968; and (3) 1969 to 1971; the second cohort: (1) 1975 to 1980; (2) 1975 to 1984; (3) 1975 to 1980; and (4) 1981 to 1984; and the third cohort: (1) 1985 to 1990; (2) 1985 to 1994; (3) 1985 to 1990; and (4) 1985 to 1989. Participants in the first, second, and third cohorts were 5555 (2336 men, 3219 women), 10 167 (4016 men, 6151 women), and 11 997 (4738 men, 7259 women), respectively. The census populations of the 40- to 69-year-old age group in each fourth community were: (1) 1966 in 1965, 2291 in 1975, and 2452 in 1985; (2) 2382 in 1965, 5538 in 1980, and 8528 in 1990; (3) 3356 in 1970, 3599 in 1975, and 4821 in 1985; and (4) 5408 in 1980 and 5729 in 1985. The participation rates in the first, second, and third cohorts were 95%, 68%, and 62%, respectively. After exclusion of the participants with a history of stroke or coronary heart disease at baseline, analyzed subjects in the first, second, and third cohorts were 5439 (2270 men, 3169 women), 9945 (3875 men, 6070 women), and 11 788 (4599 men, 7189 women), respectively.

Follow-Up and Ascertainment of Cases

Follow-up lasted until the end of 1978 for the first cohort, the end of 1990 for the second cohort, and the end of 1997 for the third cohort to determine the first incident of stroke, exit from the community, or death. Mean follow-up years were 10.3 years, 10.4 years, and 10.2 years, respectively.

The details of end point determination have been reported elsewhere.14 Cases with stroke as an underlying cause of death (International Classification of Diseases, 9th Revision, code 430–438) were selected from death certificates. We also used national insurance claims, ambulance records, reports by local physicians, as well as reports by public health nurses and health volunteers. For confirmation of the diagnosis, all living patients were either telephoned or visited to obtain their medical history in addition to a review of their medical records. For deaths, we obtained histories from families and reviewed medical records.

Stroke was defined as a focal neurological disorder with rapid onset and persisting for at least 24 hours or until death. Based on this clinical criterion, the incidence of strokes was determined by a panel on onset and persisting for at least 24 hours or until death. Based on this review of their medical records. For deaths, we obtained histories as reports by public health nurses and health volunteers. For national insurance claims, ambulance records, reports by local physicians, as well as reports by public health nurses and health volunteers. For confirmation of the diagnosis, all living patients were either telephoned or visited to obtain their medical history in addition to a review of their medical records. For deaths, we obtained histories from families and reviewed medical records.

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Baseline Examination

Systolic and fifth-phase diastolic blood pressures in the right arm were measured by trained physicians using standard mercury sphygmomanometers with a cuff 14 cm wide and 51 cm long on the unified epidemiological methods.11,17 The participants were seated and had rested for 5 minutes before the measurements. The blood pressure measurement has been repeated after 5 deep breath when systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg since the 1980s. In the present study, the first reading was used for the long-term trend analyses.

We analyzed the data according to 2 sets of blood pressure categories, ie, 6 categories by 1999 World Health Organization–International Society of Hypertension guidelines for the management of hypertension1 and other guidelines.2,3,5 and 4 categories by the seventh report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure.4

We calculated body mass index and obtained the Minnesota code, second version18 from standard 12-lead electrocardiograms (ECG) coded by 2 trained physician epidemiologists.

Serum total cholesterol was measured with the Zac-Henly method19 for the 1963 to 1974 period, with the Liebermann-Burchard direct method using Autoanalyzer II (Technicon) for 1974 to 1979, Autoanalyzer SMA-6/60 (Technicon) used for 1979 to 1986, the enzymatic method using Autoanalyzer SMAC (Technicon) used for 1986 to 1993, and Autoanalyzer Hitachi 7250 (Hitachi) used for 1993 to 1994. All measurements were performed at the laboratory of the Osaka Medical Center for Health Science and Promotion, an international member of the US National Cholesterol Reference Method Laboratory Network.20

Statistical Analysis

Analysis of covariance was used to test differences in age- and sex-adjusted means and proportions of baseline characteristics by blood pressure category. Hazard ratios and 95% CI for total stroke were calculated with the aid of Cox proportional hazards regression models. The referent was optimal blood pressure category at baseline. The hazard ratios of normal blood pressure, high normal blood pressure, mild hypertension, moderate hypertension, and severe hypertension were then determined. The initial model was adjusted only for age and sex, whereas the multivariable adjustment included age, sex, baseline body mass index category (quartiles of each period), serum total cholesterol category (quartiles of each period), ischemic ECG findings, and left ventricular hypertrophy: Minnesota code 1-3, or 4-1 to 4-3, or 5-1 to 5-3, or 7-1, and Minnesota code 3-1 and (4-1 to 4-3 or 5-1 to 5-3)21 for atrial fibrillation, antihypertensive medication use, and communities.

The PAF, the proportion of disease events in the population that would be attributable to a particular risk factor, was calculated. A PAF can be quantitatively partitioned into exposure category–specific attributable fractions, which sum to the PAF. We used a category-specific attributable fraction with the formula of pdi(1/RRR), which produces internally valid estimate when confounding exists,22 where pdi represents the proportion of total events in the population arising from the ith exposure category and RRI is the multivariable adjusted hazard ratio for the ith exposure category relative to the unexposed group. We also calculated approximative estimates of 95% CI for the PAF.23 The sum of the category-specific attributable fractions is i pdi(1/RRI). PAF is expressed as a percentage. All statistical analyses were performed with the SAS System for Windows (version 9.1; SAS Inc). All probability values for statistical tests were 2-tailed, and values of P<0.05 were regarded as statistically significant.

Results

Table 1 shows the baseline characteristics in terms of the blood pressure categories of the 3 cohorts. Mean of age, the proportion of antihypertensive medication use, ischemic ECG findings, or left ventricular hypertrophy were higher, and
Table 1. Age- and Sex-Adjusted Baseline Risk Characteristics by Blood Pressure Category for 3 Cohorts of Japanese Subjects Aged 40–69 Years

<table>
<thead>
<tr>
<th></th>
<th>Optimal BP</th>
<th>Normal BP</th>
<th>High-Normal BP</th>
<th>Mild HT</th>
<th>Moderate HT</th>
<th>Severe HT</th>
<th>( P )</th>
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<td>First cohort</td>
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<td>134</td>
<td>146</td>
<td>164</td>
<td>190</td>
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<td>Median DBP, mm Hg</td>
<td>68</td>
<td>76</td>
<td>80</td>
<td>84</td>
<td>94</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>50.2 (0.3)</td>
<td>51.0 (0.3)</td>
<td>52.9 (0.2)</td>
<td>55.1 (0.2)</td>
<td>57.2 (0.3)</td>
<td>57.7 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.5 (0.1)</td>
<td>22.2 (0.1)</td>
<td>22.7 (0.1)</td>
<td>23.2 (0.1)</td>
<td>23.6 (0.1)</td>
<td>24.0 (0.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>3.28 (0.07)</td>
<td>3.30 (0.07)</td>
<td>3.58 (0.06)</td>
<td>3.48 (0.06)</td>
<td>3.80 (0.08)</td>
<td>3.92 (0.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic ECG findings,* %</td>
<td>7.1 (1.2)</td>
<td>8.3 (1.1)</td>
<td>9.0 (0.9)</td>
<td>15.7 (0.9)</td>
<td>23.7 (1.4)</td>
<td>40.5 (1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy,† %</td>
<td>1.0 (0.7)</td>
<td>2.3 (0.7)</td>
<td>2.2 (0.6)</td>
<td>5.4 (0.6)</td>
<td>10.1 (0.9)</td>
<td>23.7 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>1.6 (0.5)</td>
<td>0.9 (0.5)</td>
<td>0.8 (0.4)</td>
<td>1.8 (0.5)</td>
<td>2.4 (0.8)</td>
<td>3.0 (1.3)</td>
<td>0.21</td>
</tr>
<tr>
<td>Antihypertensive medication use, %</td>
<td>1.1 (0.9)</td>
<td>2.6 (0.8)</td>
<td>4.2 (0.7)</td>
<td>10.4 (0.7)</td>
<td>19.4 (1.0)</td>
<td>19.8 (1.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Second cohort</td>
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<td></td>
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<tr>
<td>N</td>
<td>1885</td>
<td>1774</td>
<td>1923</td>
<td>2609</td>
<td>1280</td>
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<td>Men/women</td>
<td>586/1299</td>
<td>676/1098</td>
<td>724/1199</td>
<td>1112/1497</td>
<td>540/740</td>
<td>237/237</td>
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<td>110</td>
<td>124</td>
<td>134</td>
<td>146</td>
<td>164</td>
<td>186</td>
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<td>Median DBP, mm Hg</td>
<td>70</td>
<td>76</td>
<td>80</td>
<td>88</td>
<td>96</td>
<td>104</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>49.4 (0.2)</td>
<td>50.9 (0.2)</td>
<td>52.6 (0.2)</td>
<td>55.1 (0.2)</td>
<td>56.6 (0.2)</td>
<td>57.0 (0.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>21.8 (0.1)</td>
<td>22.8 (0.1)</td>
<td>23.2 (0.1)</td>
<td>23.9 (0.1)</td>
<td>24.3 (0.1)</td>
<td>24.3 (0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>4.77 (0.02)</td>
<td>4.90 (0.02)</td>
<td>4.93 (0.02)</td>
<td>4.96 (0.02)</td>
<td>4.97 (0.03)</td>
<td>4.93 (0.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic ECG findings,* %</td>
<td>4.1 (0.6)</td>
<td>4.6 (0.6)</td>
<td>7.1 (0.6)</td>
<td>8.2 (0.5)</td>
<td>14.5 (0.8)</td>
<td>22.0 (1.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy,† %</td>
<td>1.0 (0.4)</td>
<td>0.6 (0.4)</td>
<td>1.8 (0.4)</td>
<td>2.5 (0.3)</td>
<td>5.9 (0.4)</td>
<td>12.5 (0.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>0.7 (0.2)</td>
<td>1.1 (0.2)</td>
<td>0.6 (0.2)</td>
<td>0.7 (0.2)</td>
<td>0.2 (0.2)</td>
<td>0.5 (0.4)</td>
<td>0.12</td>
</tr>
<tr>
<td>Antihypertensive medication use, %</td>
<td>3.0 (0.7)</td>
<td>4.2 (0.7)</td>
<td>6.8 (0.7)</td>
<td>17.5 (0.6)</td>
<td>27.0 (0.9)</td>
<td>36.1 (1.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Third cohort</td>
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<td>N</td>
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<td>2239</td>
<td>2284</td>
<td>2849</td>
<td>1363</td>
<td>507</td>
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<tr>
<td>Median SBP, mm Hg</td>
<td>110</td>
<td>124</td>
<td>134</td>
<td>146</td>
<td>164</td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>Median DBP, mm Hg</td>
<td>68</td>
<td>76</td>
<td>82</td>
<td>88</td>
<td>96</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Age, yr</td>
<td>50.5 (0.2)</td>
<td>51.5 (0.2)</td>
<td>53.1 (0.2)</td>
<td>55.7 (0.2)</td>
<td>56.0 (0.2)</td>
<td>56.3 (0.4)</td>
<td>&lt;0.001</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>22.1 (0.1)</td>
<td>22.8 (0.1)</td>
<td>23.4 (0.1)</td>
<td>23.9 (0.1)</td>
<td>24.4 (0.1)</td>
<td>24.5 (0.1)</td>
<td>&lt;0.001</td>
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<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>4.96 (0.02)</td>
<td>5.00 (0.02)</td>
<td>5.11 (0.02)</td>
<td>5.16 (0.02)</td>
<td>5.22 (0.02)</td>
<td>5.21 (0.04)</td>
<td>&lt;0.001</td>
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<tr>
<td>Ischemic ECG findings,* %</td>
<td>5.0 (0.5)</td>
<td>5.1 (0.5)</td>
<td>6.6 (0.5)</td>
<td>8.2 (0.5)</td>
<td>11.2 (0.7)</td>
<td>14.2 (1.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left ventricular hypertrophy,† %</td>
<td>0.7 (0.3)</td>
<td>1.5 (0.3)</td>
<td>1.6 (0.3)</td>
<td>2.2 (0.3)</td>
<td>3.2 (0.4)</td>
<td>6.6 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>0.7 (0.1)</td>
<td>0.5 (0.1)</td>
<td>0.4 (0.1)</td>
<td>0.5 (0.1)</td>
<td>0.3 (0.2)</td>
<td>0.2 (0.3)</td>
<td>0.58</td>
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<tr>
<td>Antihypertensive medication use, %</td>
<td>3.4 (0.6)</td>
<td>6.5 (0.7)</td>
<td>9.9 (0.6)</td>
<td>17.6 (0.6)</td>
<td>24.1 (0.8)</td>
<td>26.7 (1.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; HT, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Data show age- and sex-adjusted means or percentage values. Numbers in parentheses indicate standard errors.

*Minnesota code: 1-3 or 4-1 to 4-3, or 5-1 to 5-3, or 7-1.
†Minnesota code: 3-1 and (4-1 to 4-3 or 5-1 to 5-3).
body mass index tended to be higher for the higher blood
pressure categories. Serum total cholesterol level also tended
to be higher for the higher blood pressure categories, but this
trend did plateau over the mild hypertension category in each
of the second and the third cohorts. There was no significant
difference in the prevalence of atrial fibrillation among the
blood pressure categories in any of the cohorts.

In each category of blood pressure, the proportion of
ischemic ECG findings or left ventricular hypertrophy de-
creased in each of blood pressure categories between the first
cohort and second cohorts; in moderate and severe hyperten-
sion, that proportion decreased further between the second
and third cohorts. The proportion of antihypertensive med-
cation use increased in each category of blood pressure
among the first, second, and third cohorts. The exception was
a stable change of the medication proportion in moderate
hypertension (from 36% to 27%) between the second and
third cohorts.

Table 2 shows sex- and age-specific incidence rates of total
stroke, hemorrhagic stroke (intracerebral and subarachnoid hemorrhages), and ischemic stroke in 3 cohorts. The inci-
dence rates declined from the first to the third cohort for each
of sex and age groups and total subjects. The proportions of
hemorrhagic stroke were slightly increased whereas those of
ischemic stroke slightly declined through 3 cohorts, ie, 26%,
27%, and 30% for hemorrhagic stroke, and 65%, 61%, and
59% for ischemic stroke.

Table 3 shows the incidence, hazard ratio, and PAF of
stroke according to the blood pressure categories of the 3
cohorts. Age- and sex-adjusted incidence of stroke declined
time: 4.6, 3.6, and 2.7 per 1000 person-year for the 3
periods, from the earliest to the latest, respectively. Each
cohort showed a striking increase in the incidence of stroke
for the higher blood pressure categories. Age- and sex-
adjusted hazard ratios increased even within the nonhyper-
tension categories of each of the cohorts. In the first cohort,
the optimal and normal blood pressure categories showed no
difference in the risk of stroke, but the risk was higher in the
high normal blood pressure category. In the second and third
cohorts, however, subjects in the normal blood pressure
category had ≈2-fold higher hazard ratio of stroke than those
in the optimal blood pressure category. Multivariable adjust-
ment attenuated these hazard ratios, but they remained
statistically significant in the third cohort. The exclusion of
≈10% of the subjects who used antihypertensive medication
did not alter the results substantially (see supplemental Tables
I and II, available online at http://stroke.ahajournals.org). We
also examined the association between surrogate markers for
hypertensive end-organ damage and risk of total stroke: the
multivariable hazard ratios were 2.6 (95% CI, 1.0–6.7), 4.0
(95% CI, 2.4–6.8), and 4.2 (95% CI, 2.2–8.0) for atrial fibrillation in the first, second, and third cohort, respectively.
The multivariable hazard ratios were and 1.5 (95% CI,
1.1–2.0), 1.7 (95% CI, 1.3–2.2), and 1.9 (95% CI, 1.4–2.6)
for ischemic ECG findings or left ventricular hypertrophy,
respectively.

The PAF of each blood pressure category from normal
blood pressure to severe hypertension was 0.3% (nonsignif-
ificant), 11%, 17%, 19%, and 20% in the first cohort, 3%, 8%,
26%, 24%, and 14% in the second cohort, and 6%, 5%, 23%,
11%, and 9% in the third cohort, respectively. The PAF of
severe hypertension and moderate hypertension accounted for
more than half of total PAF in the first cohort. Compared with
the first cohort, the PAF of severe hypertension decreased,
whereas the PAF of mild and moderate hypertension in-
creased and accounted for more than half of total PAF in the
second cohort. Compared with the second cohort, the PAF of
moderate and severe hypertension decreased in the third
cohort. The PAF of mild hypertension also decreased slightly,
but it remained the highest among all of the blood pressure
categories.

After exclusion of the subjects on antihypertensive medi-
cation, the PAF of moderate and severe hypertension did not
change materially, with the PAF of each of the blood pressure
categories at 0.1% (nonsignificant), 12%, 18%, 17%, and
18% in the first cohort, 3%, 10%, 25%, 21%, and 12% in the
second cohort, and 4%, 5%, 19%, 15%, and 10% in the third
cohort, respectively (not shown in the Tables). The trend for
PAF of blood pressure categories was similar between hem-
orrhagic and ischemic strokes; the peak of PAF of blood pressure categories similarly shifted from the severe hypertension to the mild one (see supplemental Tables I and II).

When we used the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure criteria, we observed similar trends. The peak of PAF of blood pressure categories for stroke shifted from the hypertension stage 2 in the former 2 cohorts to the hypertension stage 1 in the third cohort. The PAF of the normal blood pressure category increased steadily from the first to the third cohorts.

**Discussion**

We demonstrated first that the peak of PAF of blood pressure categories for incidence of stroke shifted from the severe hypertension in the first 1960s cohort to the mild one in the later 2 cohorts, along with the declined proportion of severe and moderate hypertension.

The blood pressure decline was attributable in part to improvement of hypertension control by antihypertensive medication as described previously. In this study, the proportions of antihypertensive medication use in persons belonged to the lowest 3 blood pressure categories steadily increased over the past 3 decades, and the persons who belonged to hypertension may shift to the lower blood pressure categories with the penetration of antihypertensive medication, which paralleled an increase in the PAF of lower blood pressure categories.

However, after exclusion of the subjects on antihypertensive medication, the result did not change materially.

<table>
<thead>
<tr>
<th>Survey Years</th>
<th>Total</th>
<th>Optimal BP</th>
<th>Normal BP</th>
<th>High-Normal BP</th>
<th>Mild HT</th>
<th>Moderate HT</th>
<th>Severe HT</th>
</tr>
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<tbody>
<tr>
<td>N at risk</td>
<td>5439</td>
<td>851</td>
<td>1024</td>
<td>1258</td>
<td>1314</td>
<td>624</td>
<td>368</td>
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<td>Person-years</td>
<td>56 012</td>
<td>8881</td>
<td>10 910</td>
<td>12 761</td>
<td>13 501</td>
<td>6318</td>
<td>3642</td>
</tr>
<tr>
<td>N of cases (the proportion of cases, %)</td>
<td>258 (100)</td>
<td>9 (3)</td>
<td>13 (5)</td>
<td>46 (18)</td>
<td>67 (26)</td>
<td>62 (24)</td>
<td>61 (24)</td>
</tr>
<tr>
<td>Person-years</td>
<td>4.6</td>
<td>1.3</td>
<td>1.4</td>
<td>3.9</td>
<td>4.4</td>
<td>9.1</td>
<td>13.9</td>
</tr>
<tr>
<td>N at risk</td>
<td>9945</td>
<td>1885</td>
<td>1774</td>
<td>1923</td>
<td>2609</td>
<td>1280</td>
<td>474</td>
</tr>
<tr>
<td>Person-years</td>
<td>102 945</td>
<td>20 027</td>
<td>18 693</td>
<td>20 313</td>
<td>26 896</td>
<td>12 649</td>
<td>4368</td>
</tr>
<tr>
<td>N of cases (the proportion of cases, %)</td>
<td>367 (100)</td>
<td>12 (3)</td>
<td>24 (7)</td>
<td>46 (13)</td>
<td>124 (34)</td>
<td>102 (28)</td>
<td>59 (16)</td>
</tr>
<tr>
<td>Age- and sex-adjusted incidence, per 1000 person-years</td>
<td>3.6</td>
<td>0.8</td>
<td>1.6</td>
<td>2.3</td>
<td>4.2</td>
<td>6.8</td>
<td>11.2</td>
</tr>
<tr>
<td>Age- and sex-adjusted HR (95% CI)</td>
<td>Reference</td>
<td>1.1 (0.5–2.6)</td>
<td>2.9 (1.4–6.0)</td>
<td>3.5 (1.7–7.0)</td>
<td>6.0 (3.0–12.2)</td>
<td>9.9 (4.9–20.0)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.83</td>
<td>0.003</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PAF (95% CI), %</td>
<td>11 (5–18)</td>
<td>17 (9–25)</td>
<td>19 (12–25)</td>
<td>20 (14–26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N at risk</td>
<td>11 788</td>
<td>2546</td>
<td>2239</td>
<td>2284</td>
<td>2849</td>
<td>1363</td>
<td>507</td>
</tr>
<tr>
<td>Person-years</td>
<td>120 325</td>
<td>26 103</td>
<td>22 936</td>
<td>23 494</td>
<td>28 962</td>
<td>13 860</td>
<td>4971</td>
</tr>
<tr>
<td>N of cases (the proportion of cases, %)</td>
<td>330 (100)</td>
<td>23 (7)</td>
<td>42 (13)</td>
<td>46 (14)</td>
<td>119 (36)</td>
<td>60 (18)</td>
<td>40 (12)</td>
</tr>
<tr>
<td>Person-years</td>
<td>2.7</td>
<td>1.1</td>
<td>2.0</td>
<td>1.9</td>
<td>3.5</td>
<td>3.8</td>
<td>7.4</td>
</tr>
<tr>
<td>Age- and sex-adjusted HR (95% CI)</td>
<td>Reference</td>
<td>1.9 (0.9–3.8)</td>
<td>3.0 (1.6–5.8)</td>
<td>5.3 (2.9–9.6)</td>
<td>8.5 (4.7–15.6)</td>
<td>13.7 (7.3–25.6)</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.072</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>PAF (95% CI), %</td>
<td>3 (0–6)</td>
<td>8 (4–12)</td>
<td>26 (19–33)</td>
<td>24 (18–29)</td>
<td>14 (10–18)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP indicates blood pressure; HT, hypertension; HR, hazard ratio; CI, confidence interval; PAF, population attributable fraction. Multivariate adjusted for age, sex, body mass index category, serum total cholesterol category, ischemic ECG findings and/or left ventricular hypertrophy, atrial fibrillation, antihypertensive medication use and communities.
the blood pressure decline was attributable mainly to increased proportion of lower hypertension categories because of large changes in diets and other lifestyles with economic growth, such as a substantial reduction of sodium intake and extremely strenuous labor as farm work and an improvement of house heating. In our previous report, we compared blood pressure levels of untreated offspring and parents when both were 40 to 49 years old, and found that blood pressure levels were significantly lower in the offspring than in parents. These suggested that improvements in environments and lifestyles may be important contributing factors for the decline of blood pressure levels.

It is noteworthy that the proportions of antihypertensive medication among persons with moderate and severe hypertension declined from the second to the third cohorts. Concurrently, there was the reduced proportion of ischemic ECG findings or left ventricular hypertrophy among persons with moderate and severe hypertension. Thus, we assume that persons with moderate and severe hypertension in the third cohort were less likely to be judged to need medication by clinicians.

Further, the three 10-year cohort studies from the 1960s, 1970s, and 1980s confirmed that higher blood pressure categories entail a higher risk of stroke even for nonhypertension categories. No difference in the risk of stroke between optimal and normal blood pressure categories was evident in the former 2 cohorts. However, in the third cohort, the normal blood pressure category had a significant almost 2-fold higher hazard ratio of stroke than the optimal category. A few population-based prospective studies have investigated the incidence of stroke according to three subclassifications of blood pressure in the nonhypertension level among Asian populations, but the difference of relative risk between optimal and normal blood pressure categories was not clear in those studies, probably because of the smaller population size. This study showed significantly higher risk of stroke for normal blood pressure than for optimal blood pressure. Further, the PAF of normal blood pressure increased and the PAF of high-normal blood pressure decreased overtime.

The total PAF of normal and higher blood pressure categories were 67%, 75%, and 54% in the first, second, and third cohorts, respectively, i.e., more than half of the occurrences of stroke were attributable to blood pressure over optimal level for the whole population. The decrease in total PAF along with the decrease in hazard ratios between the second and the third cohorts speculate the possibility that the contribution of other risk factors such as glucose abnormality or metabolic syndrome may increase. The improvements of lifestyles and accessibility to preventive medical treatment over time may also contribute to that decrease.

The increasing stroke burden under mild hypertension supports the importance of their control. A recent clinical trial demonstrated that the pharmacological treatment for high-normal blood pressure reduced the risk of incident hypertension. However, it is controversial whether pharmacological treatment should be recommended over optimal blood pressure levels because of potential problems for cost-benefit, compliance, and adverse effects. More extensive intervention trials are needed to examine this issue. Health education is necessary because blood pressure increases the risk of stroke in those with even nonhypertension levels, and the contribution of mild hypertension is becoming large.

The strengths of the present study includes the large population-based sample of middle-aged Japanese men and women in 3 cohorts of 4 communities over 30 years, and the measurement of cardiovascular risk factors has been standardized by the same research institute. To avoid changes in detection for stroke incidence with time attributable to the spread and improvements of imaging studies and other diagnostic procedures, we have used the consistent ascertainment system with the same diagnostic criteria anchored by clinical symptoms throughout all study periods.

Our study has several limitations. First, we used the first reading of blood pressure measurement to analyze the data consistently through 3 cohorts. Thus, blood pressure levels may be overestimated compared with usual values. Second, the participant rate has decreased in the second and third cohorts. Because the participants were generally more health conscious and had healthier lifestyles for prevention of cardiovascular diseases, we speculate that blood pressure levels in the second and third cohorts may be underestimated compared with real values in general populations. Third, we did not include smoking as a covariate because we did not have the data in the first cohort. However, this is unlikely to have had a major impact on our findings because the results did not change substantially when we adjusted for smoking in the second and third cohorts. Fourth, the population is limited to middle-aged subjects, and thus it is uncertain whether our findings are applicable to the other age groups. Finally, the PAF does not necessarily imply to what extent stroke events really will be prevented if the level of blood pressure would be shifted to lower categories, because other risk factors might affect the risk of stroke.

Conclusion

The higher risk of stroke incidence with higher blood pressure levels even in nonhypertension categories and the shift of stroke burden from severe/moderate hypertension to mild hypertension support the early management of hypertension and primary prevention of high blood pressures for the prevention of stroke.

Acknowledgments

The authors thank Emeritus Professor Yoshio Komachi (University of Tsukuba), Professor Minoru Iida (Kansai University of Welfare Sciences), Emeritus Professor Masamitsu Konishi (Ehime University School of Medicine), Professor Yoshihiko Naito (Mukogawa Women’s University), Dr Tomonori Okamura (National Cardiovascular Center), and Dr Yuko Nakagawa (Fujiidera Public Health Center) for their support in conducting long-term cohort studies. The authors also thank the clinical laboratory technologists, public health nurses, engineers of the computer processing unit, nurses, and nutritionists in the Department of Epidemiology and Mass Examination, Osaka Medical Center for Cancer and Cardiovascular Diseases, for their expert help.

Sources of Funding

This study was supported in part by a Grant-in-Aid for Scientific Research A (04304036, 15659146) and Research B (06454234, 08457125, 11470103) from the Japan Society for the Promotion of Science.控制器的设置。
of Science, and a 2002 scientific grant from Health Promotion Foundation.

Disclosures

None.

References

Trends for Blood Pressure and Its Contribution to Stroke Incidence in the Middle-Aged Japanese Population: The Circulatory Risk in Communities Study (CIRCS)
Hironori Imano, Akihiko Kitamura, Shinichi Sato, Masahiko Kiyama, Tetsuya Ohira, Kazumasa Yamagishi, Hiroyuki Noda, Takeshi Tanigawa, Hiroyasu Iso and Takashi Shimamoto

Stroke. 2009;40:1571-1577; originally published online April 2, 2009; doi: 10.1161/STROKEAHA.108.538629
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:
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