Validity of the JNC VI Recommendations for the Management of Hypertension in a General Population of Japanese Elderly

The Hisayama Study

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Background: It is not known whether the treatment recommendations presented in the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure are applicable to the Japanese elderly population.

Methods: We followed up 588 cardiovascular disease-free residents of a Japanese community who were 60 years or older from November 1, 1961, through October 31, 1993. Treated hypertensive patients were excluded from the analysis. During this period, CVD occurred in 179 subjects. The incidences were estimated by the pooling of repeated observations method.

Results: The age- and sex-adjusted incidences of cardiovascular disease significantly increased with elevated blood pressure levels. The hazard ratio for stage 3 hypertension was 5.34 (95% confidence interval, 2.66-10.71; \( P < 0.001 \)) compared with optimal blood pressure after adjustment for other covariates. Among subjects aged 60 to 79 years, the incidences for stages 1 through 3 hypertension were significantly higher than for those with optimal and normal blood pressure. In comparison, among those 80 years or older, the incidence was significantly higher only in patients with stage 3 hypertension. We further estimated the incidences according to the risk stratification system. In the younger elderly subjects, the incidences increased with rising blood pressure levels in each risk stratum. Similar relationships were not observed among the older elderly subjects.

Conclusions: Our findings demonstrate that the recommendations of the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure were potentially applicable to the Japanese elderly subjects 79 years or younger. Based on our findings, however, hypertension might not be a risk factor for cardiovascular disease among very old hypertensive patients with advanced atherosclerosis.

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THE SIXTH REPORT of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) recommended consideration of patient-specific estimates of absolute (rather than relative) risks for cardiovascular disease (CVD) in treatment decisions.\(^1\) For the first time, the JNC VI proposed a risk stratification system that was based not only on the level of blood pressure (BP) but also on the presence or absence of target organ damage (TOD) or other risk factors such as smoking, dyslipidemia, and diabetes. A prospective cohort study of National Health and Nutrition Examination Survey I demonstrated an absolute benefit derived from treating hypertension according to this risk stratification system in the US population.\(^2\) It is unknown whether this system works well in the Japanese elderly population.

The therapeutic guidelines of the Research Group for Long-term Prognosis of Hypertension in the Elderly were published in Japan in 1999.\(^3\) The JNC VI\(^1\) and Japanese guidelines\(^3\) are generally in accord with regard to the principles of drug prescription. However, a serious discrepancy exists between these 2 sets of guidelines on the level of BP at which antihypertensive treatment should be initiated. Among patients 70 years or older, the systolic BP levels at which antihypertensive treatment is recommended are 20 to 40 mm Hg higher in the Japanese guidelines\(^3\) than in the JNC VI.\(^1\) It is not clear which recommendation is better for the Japanese elderly population.

To clarify this issue, we examined the contribution of hypertension to risk for
CVD occurrence in a general population of Japanese elderly subjects not taking antihypertensive medication and evaluated whether the JNC VI treatment recommendations were applicable.

METHODS

STUDY DESIGN

The Hisayama Study is an ongoing population-based epidemiological study designed to investigate the morbidity and mortality of CVD and its risk factors in the town of Hisayama, Japan.4-9 At the initial screening in 1961, 588 subjects 60 years or older, all of whom were free of CVD, were registered as a cohort population, which included almost 90% of the total population of this age group. Subsequent examinations were conducted in 1967, 1974, 1978, 1983, and 1988. The response rates for these examinations were 91.8%, 90.9%, 85.9%, 74.2%, and 81.4% of CVD-free survivors, respectively. Because this report focuses on the incidence of CVD in subjects who were not taking antihypertensive medication, we excluded treated hypertensive patients from the analysis at each examination (22, 82, 45, 27, 12, and 9 subjects, respectively).

At each examination, we collected medical and life histories, conducted a physical examination and urinalysis for protein and sugar levels, measured levels of serum cholesterol, and performed electrocardiography (ECG). Information on antihypertensive treatment, smoking habits, and alcohol intake was obtained using a standard questionnaire, and these factors were classified as habitual or not. Blood pressure was measured 3 times with the subject in the recumbent position, after having rested for at least 5 minutes, by means of the standard sphygmomanometer with a standard cuff. Korotkoff phase 5 was taken as the diastolic BP unless the sounds persisted at 0, in which case Korotkoff phase 4 was recorded. The mean of 3 measurements was used in the present analysis. Body weight and height were measured with the subject in light clothing without shoes, and body mass index (calculated as weight in kilograms divided by the square of height in meters) was determined. Serum cholesterol level was determined by the Zak-Heny method, including a modification by Yoshikawa, in 1961 and 1967; by the Zorkowski method in 1974; and by the enzymatic method in 1978, 1983, and 1988.5,10 Glucose intolerance was determined by means of an oral glucose tolerance test in subjects with glycosuria in 1961 and 1967; by means of fasting and postprandial glucose concentrations in 1974, 1978, and 1983; and by means of a 75-g oral glucose tolerance test in 1988, in addition to the medical history of diabetes.7,8 Electrocardiographic abnormalities were determined as Minnesota codes 3-1 (high R-waves), 4-1, 4-2, and/or 4-3 (ST-segment depression).

BP CLASSIFICATION AND RISK STRATIFICATION

The JNC VI recommended treating hypertension according to risk stratification system based on BP categories and risk groups (A-C).1 We used the following BP categories: optimal (systolic BP [SBP], <120 mm Hg and diastolic BP [DBP], <80 mm Hg), normal (SBP, 120-129 or DBP, 80-84), high-normal (SBP, 130-139 or DBP, 85-89), stage 1 (SBP, 140-159 or DBP, 90-99), stage 2 (SBP, 160-179 or DBP, 100-109), and stage 3 (SBP, ≥180 or DBP, ≥110). In our study, risk group B included patients who did not have T0D or glucose intolerance, but had 1 or more risk factors, such as 60 years or older, sex (men and postmenopausal women), dyslipidemia, or a smoking habit. Risk group C included subjects who had T0D such as ECG abnormalities and proteinuria, or glucose intolerance. Since our subjects had at least 2 risk factors (age and sex), all of them were categorized in risk group B or C.

END-POINT DEFINITION AND ASCERTAINMENT

The subjects were followed up prospectively from November 1, 1961, through October 31, 1993, by means of repeated health examinations or a daily monitoring system established by the study team and local physicians or by members of the local health and welfare office. During this period, no subjects were lost to follow-up.

Cardiovascular disease included all types of stroke and coronary heart disease (CHD). The clinical diagnosis of stroke was determined on the basis of a detailed history, results of a neurological examination, and computed tomographic findings.6 The diagnosis of CHD included acute or silent myocardial infarction and sudden cardiac death within 1 hour after the onset of acute illness. The diagnosis of CHD was based on clinical symptoms and results of ancillary diagnostic procedures, including ECG recordings, cardiac enzyme levels, echocardiography, or coronary angiography. During the follow-up period, 471 subjects who had not been taking antihypertensive medication died, and autopsies were performed on 373 (79.2%) of them. Clinical diagnoses were corrected by autopsy findings when necessary. During the follow-up period, CVD (stroke in 155 and CHD in 34) occurred in 179 subjects who were not taking antihypertensive medication.

STATISTICAL METHODS

We calculated the incidences of CVD and its subtypes by the pooling of repeated observations method.11 This technique is a generalized person-year approach that incorporates all repeated observations. By treating each examination interval as a miniature follow-up study, the method pools observations from all intervals to examine the short-term development of CVD. The incidences were compared, and relative risks were estimated by the time-dependent Cox proportional hazards model, in which risk factors were allowed to change in accordance with data from the 5 follow-up examinations.12 If subjects had missing data in the pooling of repeated observations or in the time-dependent covariate model, they were excluded from these analyses. P<.05 was considered statistically significant. Statistical analyses were performed with the SAS program package (SAS Institute Inc, Cary, NC).

RESULTS

Trends in characteristics of subjects who had not been taking antihypertensive medication are shown in Table 1. Mean age increased from 68.7 years in 1961 to 88.2 years in 1988. The frequency of male subjects declined over time. The prevalence of hypertension (stages 1-3) slightly increased from 59.9% in 1961 to 69.2% in 1988. Body mass index slightly decreased from 21.2 in 1961 to 20.4 in 1988, whereas the mean total cholesterol level increased from 159 mg/dL (4.1 mmol/L) in 1961 to 193 mg/dL (5.0 mmol/L) in 1988. The frequency of smoking habits and alcohol intake declined with advancing age. The prevalence of glucose intolerance increased from 10.2% in 1961 to 20.0% in 1983, whereas in 1988, only 3.8% of the subjects were found to be glucose intolerant. Clear trends were not found in the frequency of abnormal ECG findings or proteinuria.

Table 2 shows the age-adjusted incidences and the multivariate-adjusted hazard ratios (HRs) of CVD among BP categories by sex. In men and women, the incidences and HRs of CVD increased with rising BP levels.
The age- and sex-adjusted incidences and the multivariate-adjusted HRs of CVD among BP categories are shown in Table 3. The incidences and HRs of stroke and CHD increased with elevating BP levels. When stroke and CHD were combined as total CVD, a similar association was observed. The differences between optimal BP and stages 1 through 3 hypertension were statistically significant even after adjustment for other covariates. In the following stratified analysis, the subjects in the optimal and normal BP groups were combined and used as a reference group, because the number of subjects categorized in each group was relatively small.

To examine whether the BP-CVD relationship changes with advancing age, the sex-adjusted incidences of CVD among BP categories were compared in 3 age strata (60-69, 70-79, and ≥80 years; Figure 1). Among subjects aged 60 to 79 years, the incidences increased with rising BP levels; the differences between optimal plus normal BP and stages 1 through 3 hypertension were statistically significant. In contrast, among participants 80 years or older, subjects with stage 3 hypertension alone had significantly higher incidences than did those with optimal or normal BP. Our findings demonstrated that the BP-CVD relationships in subjects no older than 79 years were different from those in very old subjects.

We further estimated the sex-adjusted incidences of CVD according to the risk stratification system in subjects aged 60 to 79 years and in those 80 years or older (Figure 2). In the younger subjects, as expected, the incidences increased with rising BP levels in each risk group. The incidences were significantly higher among subjects who had TOD or glucose intolerance (risk group C) compared with those of their counterparts (risk group B; sex- and BP-adjusted HR, 1.64; 95% confidence interval, 1.13-2.38; P = .009). In the oldest subjects in risk group B, the incidences of CVD were higher in patients with...
stages 1 through 3 hypertension than in those with optimal, normal, or high-normal BP, although these differences were not statistically significant. In contrast, no clear association was observed between BP and CVD among the oldest subjects with TOD or glucose intolerance (risk group C); the incidences of stages 1 through 3 hypertension tended to decrease.

COMMENT

We were able to observe the natural course of untreated hypertension during a 32-year period in a general population of Japanese elderly. An additional strength is that the transition of risk factors could be taken into account in the analysis by using the pooling of repeated observations method and time-dependent Cox proportional hazards model. In this study, we found a close association between BP and CVD incidence in the Japanese elderly. In addition, findings derived from subjects no older than 79 years support the JNC VI recommendations to evaluate hypertension based on the BP level and the presence or absence of TOD or other risk factors. Our results indicate that treating hypertension according to the JNC VI risk stratification system, found useful in the US population, might be useful in the Japanese elderly population.

Mortality due to stroke and CHD are well known to be heterogeneous among populations in different countries. Genetic heterogeneity and differences in risk factors may explain the differences in the stroke- and CHD-associated mortality. In the Seven Countries Study, the mortality due to stroke in Japan was 3 times higher compared with that in the United States, and conversely, the mortality due to CHD in Japan was one third of that in the United States at the same BP level. These facts may indicate that our results from Japanese elderly subjects are applicable to the US population.

The JNC VI treatment recommendations for older patients were the same as those for younger patients. Japanese guidelines, in contrast, proposed initiating antihypertensive treatment at higher BP levels and also set...
higher-goal BP levels among patients 70 years or older than those set for younger patients. These recommendations were proposed on the basis of the results of several prospective studies. In the Helsinki Aging Study, BP was inversely correlated with mortality among individuals 75 years or older. Takagi et al evaluated the long-term prognosis of CVD in Japanese elderly subjects aged 60 to 64 years and found that CVD mortality was significantly increased among patients with systolic BP of 160 mm Hg or higher. Port et al investigated the relationship of mortality to systolic BP in the subjects in the Framingham Study by using the reduced horizontal–logistic spline model. They set a threshold at the 70th percentile of BP and concluded that the threshold increased with age. These observations may support the idea that BP levels at which to initiate antihypertensive treatment should be higher in the elderly. There are, however, several potential limitations to the findings in these studies. First, the relation between BP and events might be biased by inclusion of treated hypertensive patients. Second, hypertensive risk for CVD could be underestimated, because the outcomes of interest in these studies were total or CVD mortality, and nonfatal CVD events were not evaluated.

In the present study, we examined the contribution of hypertension to risk for CVD occurrence in Japanese elderly subjects not taking antihypertensive medication and found that among subjects no older than 79 years, the incidences were significantly higher in patients with stages 1 through 3 hypertension than in those with optimal and normal BP. In the Rotterdam Study, van den Hoogen et al examined the association of BP with the risk for myocardial infarction among subjects not using BP-lowering medication and performed subgroup analyses for subjects aged 55 to 69 and 70 to 99 years. As a result, they found that a diastolic BP of 80 mm Hg or higher increased the risk for myocardial infarction in both age groups. In some other randomized trials, the benefits of antihypertensive treatment also persisted up to 80 years of age. These data support the JNC VI recommendations to administer the same treatment to older and younger patients with hypertension.

Previous studies have demonstrated that hypertensive risk for CVD was reduced with advancing age. In subjects older than 80 years, the influence of BP on the development of CVD has been unclear. In several studies, no clear association was found between BP and CVD mortality. In contrast, a report based on the Framingham Heart Study documented significantly positive associations of BP with CVD incidence among subjects aged 75 to 94 years. A subgroup meta-analysis of randomized trials of participants 80 years or older demonstrated that antihypertensive treatment prevented 22% of major cardiovascular events. In the present study, very old subjects with stage 3 hypertension alone had significantly higher incidences of CVD than subjects with optimal or normal BP. These data suggest that among subjects older than 80 years, very high BP may be a risk factor for CVD.

To our knowledge, the JNC VI risk stratification system has not been evaluated in very old people. The findings derived from our subjects 80 years or older did not necessarily support this risk stratification system. In these oldest subjects without TOD and glucose intolerance, the incidences of CVD tended to increase with rising BP levels. However, no clear association between CVD incidences and BP levels was found in these oldest subjects with TOD or glucose intolerance. These findings cannot be considered incidental, because subjects 80 years or older contributed 26.8% of the total person-years of observation. One possible explanation is that in the oldest subjects with TOD or glucose intolerance, higher mortality due to other diseases (eg, heart failure, end-stage renal disease, or peripheral arterial disease, which is closely related to hypertension) may reduce the BP-CVD relationship. In our oldest subjects in risk group C, however, no positive association was observed between BP and non-CVD mortality (data not shown). Another explanation is that, as a result of more advanced coronary and cerebral atherosclerosis, high BP may be necessary to guarantee adequate blood flow in the myocardium and the brain in the oldest subjects with TOD or glucose intolerance. Kannel et al demonstrated that the BP-CVD mortality associations were different between the older elderly subjects with and those without CVD. These data suggest that hypertension may not be a risk factor for CVD among the oldest subjects with advanced atherosclerosis.

Several potential limitations to the findings in our study exist. The primary limitation is that the definition of BP level was based on 3 measurements of BP taken on a single day. The BP levels might have been misclassified, despite the fact that measurements of BP on a single day have been suggested to be accurate in epidemiological studies. Second, we excluded hypertensive patients who had started antihypertensive therapy, whose BP levels may have been higher. Given that these limitations might have reduced the estimate of the risk associated with high BP, the true association may be stronger than that suggested by our findings. Third, the risk stratification system we used in the present study was almost the same as, but not identical to, that of the JNC VI. However, this bias did not seem to hold the potential to alter our findings' support of the general idea of the JNC VI treatment recommendations.

The present population-based study indicated that the management of hypertension according to the JNC VI recommendations is applicable to elderly Japanese subjects up to 79 years of age. However, the beneficial effect of antihypertensive therapy for hypertensive subjects of this age, especially those with stage 1 hypertension, should be further clarified. In subjects 80 years or older with advanced atherosclerosis, on the other hand, we found no clear association of BP with CVD, which argues against the definite benefits of treating the oldest elderly patients with hypertension.

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REFERENCES


