Effects of Prehypertension and Hypertension Subtype on Cardiovascular Disease in the Asia-Pacific Region

Hisatomi Arima, Yoshitaka Murakami, Tai Hing Lam, Hyeon Chang Kim, Hirotsugu Ueshima, Jean Woo, Il Suh, Xianghua Fang, Mark Woodward, on behalf of the Asia Pacific Cohort Studies Collaboration

Abstract—The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure defined blood pressure (BP) levels of 120 to 139/80 to 89 mm Hg as prehypertension and those of ≥140/90 mm Hg as hypertension. Hypertension can be divided into 3 categories, isolated diastolic (IDH; systolic BP <140 mm Hg and diastolic BP ≥90 mmHg), isolated systolic (systolic BP ≥140 mm Hg and diastolic BP <90 mmHg), and systolic-diastolic hypertension (systolic BP ≥140 mm Hg and diastolic BP ≥90 mmHg). Although there is clear evidence that isolated systolic hypertension and systolic-diastolic hypertension increase the risks of future vascular events, there remains uncertainty about the effects of IDH. The objective was to determine the effects of prehypertension and hypertension subtypes (IDH, isolated systolic hypertension, and systolic-diastolic hypertension) on the risks of cardiovascular disease (CVD) in the Asia-Pacific Region. The Asia Pacific Cohort Studies Collaboration is an individual participant data overview of cohort studies in the region. This analysis included a total of 346570 participants from 36 cohort studies. Outcomes were fatal and nonfatal CVD. The relationship between BP categories and CVD was explored using a Cox proportional hazards model adjusted for age, cholesterol, and smoking and stratified by sex and study. Compared with normal BP (<120/80 mmHg), hazard ratios (95% CIs) for CVD were 1.41 (1.31–1.53) for prehypertension, 1.81 (1.61–2.04) for IDH, 2.18 (2.00–2.37) for isolated systolic hypertension, and 3.42 (3.17–3.70) for systolic-diastolic hypertension. Separately significant effects of prehypertension and hypertension subtypes were also observed for coronary heart disease, ischemic stroke, and hemorrhagic stroke. In the Asia-Pacific region, prehypertension and all hypertension subtypes, including IDH, thus clearly predicted increased risks of CVD. (Hypertension. 2012; 59:1118-1123.)

Key Words: prehypertension ■ hypertension ■ hypertension subtype ■ isolated diastolic hypertension ■ cardiovascular disease ■ coronary heart disease ■ stroke

Cardiovascular disease (CVD) is a leading cause of premature death and disability globally.¹,² Elevation of blood pressure (BP) is one of the most important preventable causes of CVD: ≈54% of stroke and 47% of coronary heart disease worldwide have been attributed to it.³ The relationship of BP with the risk of CVD is continuous down to such levels.⁴ Because of its high prevalence, ¹⁰,¹¹ a substantial part of the burden of CVD occurs among people with prehypertension.¹²⁻¹⁴

Hypertension is usually defined as BP levels of ≥140/90 mmHg⁷⁻⁹ and can be divided into 3 categories, isolated diastolic hypertension (IDH), isolated systolic hypertension (ISH), and diastolic with systolic hypertension (systolic-diastolic hypertension [SDH]).¹⁵ A number of observational...
studies have demonstrated clear associations of ISH and SDH with future cardiovascular events.\textsuperscript{16–21} In contrast, there has been uncertainty surrounding the effects of IDH on the risks of CVD.\textsuperscript{16–23} As a result, patients with IDH, which constitutes 14% to 24% of the total hypertensive population,\textsuperscript{18,20,24} are less likely to receive clinical attention and BP-lowering treatment than those with ISH or SDH.\textsuperscript{18–20}

The Asia Pacific Cohort Studies Collaboration (APCSC) is an individual participant data overview of cohort studies in the region.\textsuperscript{25,26} Previous studies from the APCSC have focused on the continuous effects of BP on the risk of CVD.\textsuperscript{5,6} In the present analysis, we provide detailed information about the associations between prehypertension and hypertension subtypes (IDH, ISH, and SDH) and the risk of CVD.

**Methods**

All of the APCSC cohort studies recorded date of birth (or age), sex, and BP at baseline and date of death (or age at death) during follow-up. Studies were excluded if enrollment depended on having a particular condition of a risk factor. For this report, only participants aged from 30 to 90 years at baseline with information on smoking status and total cholesterol were included. Studies were classified as Asian if participants were recruited from mainland China, Hong Kong, Japan, Korea, Singapore, Taiwan, and Thailand, and as ANZ (predominantly White) if participants were recruited from Australia or New Zealand. In most studies, BP was measured at rest in the seated position using a standard mercury sphygmomanometer.\textsuperscript{5,6} Smoking status was self-reported as never smoker, ex-smoker, or current smoker. Because the APCSC is based on existing data, no ethics approval was needed for the present study.

All of the studies reported deaths attributed to CVD; some studies also reported nonfatal CVD events, defined as events that did not result in death within 28 days. All of the analyses use pooled fatal and nonfatal outcomes, taking the first recorded event as the index event. Outcomes were classified according to the Ninth Revision of International Classification of Disease. The outcomes considered in this analysis were coronary heart disease (Ninth Revision of International Classification of Disease 410–414), hemorrhagic stroke (431.0–432.9), ischemic stroke (433.0–434.9), and total CVD (390–439). Because most studies identified events using record linkage, verification of stroke was not routinely reported. All of the data provided were checked for completeness and consistency and recoded, when necessary, to ensure maximize comparability across cohorts. Summary reports were referred back to the principal investigators of each collaborating study for review and confirmation.

Cox proportional hazard models were used to examine the effects of BP category on CVD. Baseline hazards were allowed to differ by sex and cohort by using these variables as strata in the Cox models. Age, total serum cholesterol, and smoking status were included as confounders in all of the models. BP categories were classified as normal BP (SBP <120 mm Hg and DBP <80 mm Hg), prehypertension (SBP 120–139 mm Hg and/or DBP 80–89 mm Hg), IDH (SBP <140 mm Hg and DBP <90 mm Hg), ISH (SBP ≥140 mm Hg and DBP <90 mm Hg), and SDH (SBP ≥140 mm Hg and DBP ≥90 mm Hg). Normal BP was taken as the reference category for hazard ratios (HRs). Subgroup analyses by sex, age (<65 years and ≥65 years), and region (Asia/ANZ) were performed for total CVD. Comparison of the effects of BP categories between subgroups was done by adding interaction terms to the statistical models. All of the statistical analyses were performed using SAS release 9.20 (SAS Institute Inc, Cary, NC).

**Results**

**Baseline and Follow-Up Data**

Data from 36 cohort studies, which included 346,570 participants, were included in the present analyses (Table S1, available in the online-only Data Supplement). The mean age of participants at baseline was 48 years, 41% were women, and 78% were from Asia. Percentage of BP categories was 38%, 38%, 6%, 8%, and 11% for normal BP, prehypertension, IDH, ISH, and SDH, respectively. During a mean follow-up of 7 years, 8598 people (2.5%) experienced a CVD event, 3270 (0.9%) experienced coronary heart disease, 1503 (0.4%) experienced ischemic stroke, and 1015 (0.3%) experienced hemorrhagic stroke.

**Effects of BP Category on the Risk of CVD**

Compared with normal BP, prehypertension and all of the hypertension subtypes were clearly associated with increased risks of CVD even after controlling for age, sex, cholesterol, and smoking (Figure 1). The risks of CVD increase in the order of prehypertension, IDH, ISH, and SDH ($P<0.0001$ for normal BP versus prehypertension; $<0.0001$ for prehypertension versus IDH; 0.0013 for IDH versus ISH; and $<0.0001$ for ISH versus SDH). When prehypertension was divided into isolated diastolic prehypertension (SBP $<120$ mm Hg and DBP $80$–$89$ mm Hg), isolated systolic prehypertension (SBP $120$–$139$ mm Hg and DBP $<80$ mm Hg), and systolic-diastolic prehypertension (SBP $120$–$139$ mm Hg and DBP $80$–$89$ mm Hg), HRs were $1.08$ (95% CI, 0.91–1.29), $1.42$ (1.30–1.56), and $1.47$ (1.34–1.61), respectively. Effects of prehypertension and hypertension subtypes were comparable between fatal CVD (HR, $1.33$ [95% CI, $1.20$–$1.46$] for prehypertension, $1.77$ [1.51–2.06] for IDH, $2.07$ [1.87–2.29] for ISH, and $3.16$ [2.87–3.49] for SDH) and nonfatal CVD (1.57 [1.39–1.76] for prehypertension, 2.04 [1.72–2.42] for IDH, 2.38 [2.09–2.72] for ISH, and 3.93 [3.48–4.43] for SDH). Separately, significant effects of prehypertension and hypertension subtypes were also observed for coronary heart disease, ischemic stroke, and hemorrhagic stroke (Figure 1), and the risks of each outcome increased in the order of prehypertension, IDH, ISH, and SDH (normal BP versus prehypertension, $P<0.0001$ for all; prehypertension versus IDH, $P<0.0001$ for all; IDH versus ISH, $P=0.95$, 0.0008, and 0.09 for coronary heart disease, ischemic stroke, and hemorrhagic stroke, respectively; and ISH versus SDH, $P<0.0001$ for all). The relationship of each BP category with coronary heart disease was weaker than for ischemic or hemorrhagic stroke. Between 2 stroke subtypes, the association with hemorrhagic stroke was stronger than for ischemic stroke.

Among subjects of the present analysis, a total of 121,051 participants had information on BP-lowering treatment. Compared with normal BP without treatment, number of events per subject and multivariable-adjusted HR (95% CI) for development of CVD were 1041/39,479 and 1.25 (95% CI, 1.10–1.42) for prehypertension without treatment, 106/30,28 and 1.53 (95% CI, 1.19–1.95) for IDH without treatment, 1064/30,28 and 2.38 (95% CI, 2.10–2.75) for ISH without treatment, and 1407/18,231 and 2.77 (95% CI, 2.43–3.16) for treated hypertension.

**Effects of BP Category on the Risk of Total CVD by Subgroups**

There were similar effects of prehypertension and hypertension subtypes on the risks of CVD between male and female
Discussion
Findings from the current study, based on prospective data from \( \approx 350,000 \) individuals from the Asia-Pacific region, provide good evidence of clear associations of prehypertension and all types of hypertension, including IDH, with future risks of CVD. Separately, significant associations were observed for coronary heart disease, ischemic stroke, and hemorrhagic stroke. These associations remained significant after controlling for the confounding effects of age, sex, cholesterol, and smoking. Furthermore, increased risks of CVD associated with prehypertension and hypertension subtypes were observed across subgroups defined by age, sex, and geographical region, although there was a certain degree of heterogeneity in the strength of the associations by age and region.

Large-scale observational studies have demonstrated that prehypertension is associated with increased risks of premature death and cardiovascular morbidity, particularly at BP levels of 130 to 139/85 to 89 mmHg.\(^\text{13,27-33}\) Likewise, a number of large-scale cohort studies have reported significant effects of prehypertension separately on the risks of stroke\(^\text{13,29,30,32}\) and coronary heart disease.\(^\text{13,29}\) The present analysis from the APCSC confirmed the results from the previous observational studies and provided more detailed information about the separately significant associations of prehypertension with all of the major types of CVD, including ischemic and hemorrhagic stroke in the Asia-Pacific region.

Despite the clear evidence of ISH and SDH as important predictors of future vascular events,\(^\text{16-21}\) a number of observational studies have failed to show significant effects of IDH on the risks of cardiovascular morbidity or mortality, probably because of the smaller number of subjects with IDH.\(^\text{16-19,22}\) However, 2 recent large-scale cohort studies conducted in China have demonstrated clear effects of IDH on the risks of coronary heart disease, stroke, and total CVD.\(^\text{20,21}\) The analysis reported
Figure 2. Effects of prehypertension and hypertension subtype on the risk of total cardiovascular disease by sex, age, and geographical region. Conventions are as for Figure 1.

Here supports the findings obtained from the 2 studies conducted in China and demonstrates that the effects of IDH on the risks of CVD are generalizable to Western populations, as well as Asian populations.

In the present analysis, the highest risk of CVD was observed among patients with elevated SBP and DBP (SDH). The second highest risk was among patients with ISH, and the third highest risk was among those with IDH. Similar association was observed for each of the major CVD subtypes. There was also consistency in the ranking between hypertension subtypes across subgroups defined by age, sex, and geographical region. The same ranking in the effects of hypertension subtypes was also reported from other cohort studies.19–21

The Stroke Prevention Project in China has investigated the effects of hypertension subtype on stroke among 26,587 Chinese subjects and found that HRs were 2.16 for IDH, 2.35 for ISH, and 2.73 for SDH compared with normotensives.20 Likewise, the China Hypertension Epidemiology Follow-Up Study has demonstrated that HRs of CVD incidence were 1.59 for IDH, 1.78 for ISH, and 2.73 for SDH among 169,871 participants from China.21 A prospective cohort study of 3267 men in Finland has also shown that HRs of stroke incidence were 1.14 for IDH, 1.36 for ISH, and 2.71 for SDH.19 One possible reason for lower risks of CVD in IDH may involve younger age of patients with IDH than those with ISH or SDH.16–22 These findings support the hypothesis that the risks of CVD increase in the order of IDH, ISH, and SDH.

Another key result from the present analysis was the heterogeneity in the effects of prehypertension and hypertension subtypes on different types of CVD and heterogeneity in the effects of each BP category across subgroups defined by age or geographical region. These findings are directly in line with the results of large-scale observational studies that had identified smaller effects of BP on the risks of coronary heart disease than on the risks of stroke, stronger effects of BP on intracerebral hemorrhage than on the risks of ischemic stroke, and stronger effects of BP on CVD among younger or Asian subjects compared with older or Western subjects.4,5,34 Although there were no clear effects of prehypertension on the risks of coronary heart disease versus 53 years) despite our adjustment for age, and stroke, which was more strongly associated with BP than coronary heart disease, was more common in Asian studies than in ANZ studies. Heterogeneity in the effects of each BP category across subgroups defined by age or geographical region. These findings are directly in line with the results of large-scale observational studies that had identified smaller effects of BP on the risks of coronary heart disease than on the risks of stroke, stronger effects of BP on intracerebral hemorrhage than on the risks of ischemic stroke, and stronger effects of BP on CVD among younger or Asian subjects compared with older or Western subjects.4,5,34 Although there were no clear effects of prehypertension on the risks of coronary heart disease versus 53 years) despite our adjustment for age, and stroke, which was more strongly associated with BP than coronary heart disease, was more common in Asian studies than in ANZ studies.
As far as we are aware, this is the largest study to report the effects of prehypertension and hypertension subtypes on the risks of CVD. The number of individuals involved in the present analysis of APCSC means that the overall estimates are more precise than those in most previous studies. The main weaknesses of APCSC relate to nonstandardization of data collection methods. All of the cohorts were begun before the collaboration was initiated, without a common protocol. This might have introduced variations in measurement error in determining BP levels and possible misclassification of events, particularly with respect to stroke subtype. Reliable verification of stroke subtype requires imaging or autopsy data, and although it is likely that such information formed the basis of most reporting, this could not always be confirmed.

**Perspectives**

In the Asia-Pacific region, prehypertension and all of the hypertension subtypes were significantly associated with increased risks of CVD. Because a large portion of the population is classified as prehypertension or hypertension, population strategy to lower BP at the community level, such as salt reduction in commercial products, civil engineering to facilitate walking, and a systematic large-scale educational effort, are essential for reduction in the global burden of CVD. Furthermore, BP-lowering treatment should be initiated, and target BP levels recommended by current guidelines adopted, among all patients who require drug treatment, irrespective of hypertension subtype (IDH, ISH, and SDH).

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**Disclosures**

None.

**References**


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Asia Pacific Cohort Studies Collaboration

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Table S1. Characteristics of study population

SD indicates standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; IS, ischemic stroke; HS, hemorrhagic stroke; CVD, cardiovascular disease; ANZ, Australia and New Zealand.
Figure S1. Effects of prehypertension and hypertension subtype on the risk of coronary heart disease, ischemic stroke and hemorrhagic stroke by geographical region

Hazard ratios were adjusted for age, total cholesterol and smoking and stratified by sex and study. Normal blood pressure was used as the reference group. The center of each solid box is plotted against the point estimate and the horizontal lines are drawn to the 95% confidence limits. Areas of the boxes are proportional to the reciprocal of the variance of the estimates. 95% CI indicates 95% confidence interval.
Appendix S1: Asia Pacific Cohort Studies Collaboration membership

APCSC Executive Committee

Participating Studies and Principal Collaborators in APCSC