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Hypertension. 2005;46:393-397; originally published online July 5, 2005;

doi: 10.1161/01.HYP.0000177118.46049.e6

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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Comparison of Blood Pressure–Associated Risk of Intracerebral Hemorrhage and Subarachnoid Hemorrhage Korea Medical Insurance Corporation Study

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Abstract—Intracerebral hemorrhage and subarachnoid hemorrhage have different pathogeneses and risk factor profiles. However, little information is available on the difference between intracerebral and subarachnoid hemorrhages in relation to blood pressure. We prospectively investigated the relationships between blood pressure and risks of stroke subtypes. We measured blood pressure and other cardiovascular risk factors in 100 147 men and 59 558 women 35 to 59 years of age in 1990 and 1992. Outcomes were fatal and nonfatal events of stroke and its subtypes from 1993 to 2002. Independent relationships between baseline blood pressure and stroke subtypes were assessed using Cox’s proportional hazard models. During the 10 years, 1714 ischemic and 1159 hemorrhagic strokes (742 intracerebral and 308 subarachnoid hemorrhages) occurred. Blood pressure was related more closely with hemorrhagic stroke than ischemic stroke, and the difference was more prominent in women. Among the subtypes of hemorrhagic stroke, intracerebral hemorrhage was more closely related with blood pressure than subarachnoid hemorrhage. For each 20 mm Hg increase in systolic blood pressure, adjusted relative risks of ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage were 1.79 (95% confidence interval, 1.68 to 1.90), 2.48 (2.30 to 2.68), and 1.65 (1.38 to 1.97) in men, and 1.64 (1.42 to 1.89), 3.15 (2.61 to 3.80), and 2.29 (1.82 to 2.89) in women, respectively. In conclusion, blood pressure is more closely related with intracerebral hemorrhage than subarachnoid hemorrhage, thus proportion of intracerebral hemorrhage in hemorrhagic stroke may affect the association between blood pressure and hemorrhagic stroke. Our data also emphasize the importance of blood pressure control for the prevention of stroke, especially in countries with a high incidence of intracerebral hemorrhage. (*Hypertension*. 2005;46:393-397.)

Key Words: blood pressure ■ risk factors

It is well accepted that high blood pressure plays a central role in the development of stroke, and epidemiological data repeatedly indicate positive dose-dependent relationships between blood pressure and stroke. Moreover, several studies have compared the effects of blood pressure on the risks of ischemic and hemorrhagic stroke.^{1–5} A meta-analysis of 61 prospective studies on the association between blood pressure and vascular mortality showed similar associations for ischemic and hemorrhagic stroke.⁴ In another meta-analysis of Asian populations, blood pressure level was found to be more strongly associated with hemorrhagic stroke than ischemic stroke.² A recent observation study added evidence supporting the closer relationship between blood pressure and hemorrhagic stroke than with ischemic stroke.⁵ Although many observational studies have compared ischemic and hemorrhagic stroke in relation to blood pressure level, the difference of hemorrhagic stroke subtypes in relation to blood pressure has not been fully investigated. Two different subtypes, specifically intracerebral hemorrhage (ICH) and subarach-

noid hemorrhage (SAH), account for the majority of hemorrhagic stroke,⁶ and much evidence indicates that ICH and SAH have different pathogeneses and risk factors.^{1,3,7–9} High blood pressure has been reported to be a common important risk factor for ICH and SAH,^{1,3,4,9} but there is little data comparing the blood pressure–associated risk of ICH and SAH. Thus, we investigated the nature of the relationships between blood pressure and the risks of stroke subtypes, including ICH and SAH, in a large prospective cohort study: the Korea Medical Insurance Corporation (KMIC) Study.

Methods

Study Population and Data Collection

KMIC provides health insurance to government and private school employees and their dependents. In 1990, the corporation insured 1 213 594 workers and 3 389 767 dependents, ≈11% of the total Korean population. In 1990 and 1992, 95% and 94% of the workers completed biennial health examinations, which were conducted by the corporation. The KMIC Study cohort consisted of 115 200 men (25% random sample) and 67 932 women (100% sample) 35 to 59

Received February 14, 2005; first decision March 3, 2005; revision accepted June 7, 2005.

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Hypertension is available at <http://www.hypertensionaha.org>

DOI: 10.1161/01.HYP.0000177118.46049.e6

years of age and underwent health examinations in both years. Details of the study design have been described previously.¹⁰ Data were available on blood pressure levels and major cardiovascular risk factors for 108 464 men and 64 120 women. We excluded people who indicated that they had any previously known disease at baseline and enrolled 100 147 men and 59 558 women for the analyses.

Blood pressures were measured in 1990 and 1992 by trained staff using a standard mercury sphygmomanometer (the fifth Korotkoff sound was used for diastolic pressure) or an automatic manometer, with the individual seated. Height and weight, fasting serum glucose and cholesterol, and aspartate and alanine aminotransferase levels were also measured in 1990 and 1992. The averages of 2 measurements were used for the above-mentioned variables. Data on smoking status and alcohol consumption were obtained using a self-reported questionnaire in 1992. The follow-up period spanned 10 years, from January 1993 to December 2002. The outcome variables were fatal and nonfatal events of ischemic stroke, hemorrhagic stroke, ICH, and SAH, as coded by the 9th and 10th revisions of the International Classification of Diseases. Health insurance claim data were used to ascertain nonfatal and fatal outcomes and causes of death on death certificates for fatal outcomes.

Statistical Analysis

Body mass index was calculated as body weight divided by height squared (kg/m^2) and classified into quartiles. Blood pressure level was classified according to the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: optimal, normal, high-normal, and hypertension stages 1, 2, and 3.¹¹ The categories for fasting glucose level were <6.1 , 6.1 to 6.9, and ≥ 7.0 mmol/L. The categories for serum cholesterol level were <5.2 , 5.2 to 6.1, and ≥ 6.2 mmol/L. Serum aspartate and alanine aminotransferase levels were classified into normal (<35 IU/L), moderate (35 to 69 IU/L), and high elevation (≥ 70 IU/L). Smoking was classified into 3 categories: current smokers, ex-smokers, and nonsmokers. The categories of alcohol consumption were the nondrinker, moderate drinker (<50 g per day), and heavy drinker (≥ 50 g per day). Daily alcohol intake was calculated by multiplying the frequency of drinking and the amount of drinking at once. Cox's proportional hazard models were used to calculate the relative risks of stroke subtypes according to the blood pressure level after adjustments for age and the above-mentioned variables (smoking and alcohol intake were adjusted only in men).

Results

Baseline characteristics of the 100 147 men and 59 558 women were showed (Table 1). At baseline, the male participants were older, had higher body mass index, blood pressure, fasting blood glucose, total cholesterol, and aminotransferase levels than the female participants ($P<0.01$ for all). Also, cigarette smoking and alcohol intake were more frequent in men.

During the 10 years, a total of 3187 (2550 in men and 637 in women) stroke events occurred. ICH and SAH accounted for 25% and 8% of all strokes in men, and for 18% and 17% of all strokes in women, respectively. Fatalities were highest for ICH and lowest for ischemic stroke, thus, the majority of stroke mortalities (50% in men and 38% in women) were attributable to ICH (Table 2).

Blood pressure level was found to have significant dose-response relationships with each stroke subtype, but the strength of associations were differed by the subtypes. In men, ICH was most strongly associated with blood pressure, and the associations of blood pressure with SAH and ischemic stroke were similar. ICH was also most strongly associated with blood pressure in women. Moreover, associations

TABLE 1. Baseline Characteristics in Men and Women

Baseline Characteristics	Men (n=100 147)	Women (n=59 558)
Mean (SD)		
Age, years	44.8 (6.7)	42.4 (6.2)
Body mass index, kg/m^2	23.5 (2.4)	22.3 (2.5)
Fasting blood glucose, mmol/L	5.1 (1.0)	4.8 (0.7)
Total cholesterol, mmol/L	5.0 (0.8)	4.9 (0.8)
Aspartate aminotransferase, IU/L	25.7 (13.5)	20.4 (7.9)
Alanine aminotransferase, IU/L	25.2 (16.0)	17.5 (9.3)
Systolic blood pressure, mm Hg		
In 1990	124.9 (15.1)	115.4 (13.6)
In 1992	125.5 (15.8)	116.8 (14.3)
Average	125.2 (13.9)	116.1 (12.4)
Diastolic blood pressure, mm Hg		
In 1990	81.9 (10.8)	75.2 (10.2)
In 1992	82.1 (11.0)	75.9 (10.5)
Average	82.0 (9.5)	75.5 (8.9)
No. (%)		
Cigarette smoking		
Nonsmoker	20 500 (21.4)	48 342 (99.2)
Ex-smoker	19 823 (20.6)	220 (0.5)
Current smoker	55 748 (58.0)	193 (0.4)
Alcohol consumption		
Nondrinker	22 809 (23.5)	47 136 (89.0)
<50 g/day	64 979 (67.0)	4682 (8.9)
≥ 50 g/day	9253 (9.5)	1124 (2.1)

of blood pressure with ICH and SAH were stronger in women than in men. Even when systolic and diastolic blood pressures were treated as continuous variables, similar relationships were observed (Table 3).

Discussion

In this large population-based cohort, we found that risk ratios by blood pressure level differed for ischemic and hemorrhagic stroke and also between ICH and SAH. Moreover, it appears that the strengths of associations between blood pressure and hemorrhagic stroke may be affected by the proportion of ICH in hemorrhagic stroke and by the sex distribution of the study population.

A plethora of observational studies have compared ischemic and hemorrhagic stroke in relation to blood pressure level. The Prospective Studies Collaboration (PSC) observed that the risk ratios of mortality from ischemic and hemorrhagic stroke by blood pressure level were similar, at least for those <80 years of age.⁴ However, the Eastern Stroke and Coronary Heart Disease Collaboration (ESCC) reported a stronger association between blood pressure and hemorrhagic stroke than with nonhemorrhagic stroke.² Recently, Song et al supported the closer relationship between hemorrhagic stroke and blood pressure level.⁵ Moreover, their study indicated a greater difference than the ESCC study and that shown by our data.

TABLE 2. Stroke Event Numbers for 100 147 Men and 59 558 Women Over 10 Years

Stroke Subtype	ICD-10 Code	Men		Women	
		All Events	Fatal Events	All Events	Fatal Events
Ischemic stroke	I63, I65, I66	1423 (55.8)	72 (16.3)	291 (45.7)	6 (10.0)
Hemorrhagic stroke	I60–I62	923 (36.2)	280 (63.5)	236 (37.0)	41 (68.3)
ICH	I61	628 (24.6)	220 (49.9)	114 (17.9)	23 (38.3)
SAH	I60	201 (7.9)	48 (10.9)	107 (16.8)	14 (23.3)
Other hemorrhagic stroke	I62	94 (3.7)	12 (2.7)	15 (2.4)	4 (6.6)
Unspecified	I64, I67	204 (8.0)	89 (20.2)	110 (17.3)	13 (21.7)
All stroke	I60–I67	2550 (100)	441 (100)	637 (100)	60 (100)

Numbers in the parenthesis are proportions (%) of each stroke subtype in all strokes. ICD indicates International Classification of Diseases.

There are several explanations for these inconsistencies. First, different proportions of ICH in hemorrhagic stroke could produce such inconsistent findings. The ESCC study analyzed 13 cohorts in China and Japan,² but the PSC study pooled data from 61 cohorts worldwide, largely from Western countries.⁴ The proportion of ICH in East Asian populations has been reported to be higher than in the West.⁶ Thus, the association between blood pressure and hemorrhagic stroke might be stronger in Asian populations in which ICH in hemorrhagic stroke is more common. Unlike other studies, Song et al equated ICH with hemorrhagic stroke, which may explain their strongest association between blood pressure and hemorrhagic stroke.⁵ Second, sex and age distribution considerations could have caused these inconsistencies. Relationships between blood pressure and stroke subtypes may

differ by sex and age.^{2,4,12,13} In our data, the association between blood pressure and ischemic stroke was similar in men and women, whereas the associations with ICH and SAH were stronger in women than in men. The PSC study and our study analyzed men and women separately,⁴ but the other 2 studies did not provide sex-specific results.^{2,5} The different age distributions might be another source of inconsistent findings on the associations between blood pressure and stroke subtypes.^{12,13} Thus the sex and age differences in these populations may have altered the natures of associations. Third, definitions of outcome variables provide another source of inconsistency. Outcomes in the PSC study were deaths from stroke,⁴ whereas outcomes in the other 2 studies and in our study included fatal and nonfatal events.^{2,5} Fatality of ICH is much higher than those of SAH and ischemic

TABLE 3. Independent Relationship Between Blood Pressure and the Risk of Stroke Subtypes

Blood Pressure†	Adjusted Risk Ratio* (95% Confidence Interval)			
	Ischemic Stroke	Hemorrhagic Stroke	ICH	SAH
Men				
Optimal	1.00	1.00	1.00	1.00
Normal	1.43 (1.16–1.76)	1.53 (1.16–2.01)	1.66 (1.13–2.44)	1.46 (0.89–2.38)
High-normal	1.81 (1.47–2.23)	2.38 (1.83–3.11)	2.97 (2.06–4.28)	2.41 (1.50–3.87)
Hypertension stage 1	2.82 (2.31–3.41)	3.82 (2.96–4.92)	5.42 (3.83–7.66)	2.92 (1.82–4.69)
Hypertension stage 2	3.91 (3.09–4.95)	7.04 (5.26–9.44)	11.79 (8.07–17.21)	3.66 (1.91–7.04)
Hypertension stage 3	6.58 (4.96–8.73)	15.52 (11.25–21.41)	26.86 (17.94–40.23)	5.12 (2.07–12.64)
Systolic (per 20 mm Hg)	1.79 (1.68–1.90)	2.19 (2.04–2.35)	2.48 (2.30–2.68)	1.65 (1.38–1.97)
Diastolic (per 10 mm Hg)	1.51 (1.44–1.59)	1.84 (1.74–1.94)	2.04 (1.92–2.17)	1.48 (1.29–1.70)
Women				
Optimal	1.00	1.00	1.00	1.00
Normal	1.36 (0.98–1.90)	1.87 (1.27–2.77)	2.48 (1.34–4.59)	1.77 (1.04–3.01)
High-normal	1.91 (1.34–2.72)	3.34 (2.21–5.06)	4.54 (2.38–8.65)	2.60 (1.42–4.76)
Hypertension stage 1	2.35 (1.65–3.35)	6.19 (4.17–9.18)	11.45 (6.38–20.55)	3.82 (2.08–7.03)
Hypertension stage 2	2.94 (1.74–4.98)	9.23 (5.18–16.42)	10.91 (4.41–27.02)	9.06 (4.08–20.13)
Hypertension stage 3	5.97 (3.01–11.75)	39.73 (20.52–65.35)	63.27 (28.12–142.40)	20.49 (7.59–55.33)
Systolic (per 20 mm Hg)	1.64 (1.42–1.89)	2.72 (2.36–3.13)	3.15 (2.61–3.80)	2.29 (1.82–2.89)
Diastolic (per 10 mm Hg)	1.49 (1.33–1.66)	2.17 (1.93–2.42)	2.40 (2.06–2.80)	1.96 (1.64–2.34)

*Adjusted for age, body mass index, fasting blood glucose, total cholesterol, aminotransferase, smoking (men only) and alcohol intake (men only); †categorized in accord with the guidelines of the Sixth Report of Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure.¹¹

stroke. When a study uses mortality instead of incidence, the selective inclusion of severe cases is more prominent in ischemic stroke and SAH than in ICH. Thus, differences in the strength of associations by stroke subtypes are likely to be altered if the outcome variable is mortality.

ICH and SAH, which are frequently combined into the category hemorrhagic stroke in observational studies, are separate disease entities and have different risk factor profiles.^{3,7} Thus, in studies undertaken to investigate the risk of hemorrhagic stroke, ICH and SAH must be dealt with separately. However, little prospective data are available that directly compare ICH and SAH with respect to blood pressure. Several efforts have been made to compare risk factors in ICH and SAH.^{3,14–17} These studies adopted cross-sectional or case-control designs and tried to identify different risk factors for the different subtypes. In the present study, we were able to compare blood pressure–associated risks of ICH and SAH, and the results obtained show that blood pressure is a more important risk factor in ICH. The higher relative risk of hemorrhagic stroke in those with high blood pressure might be predominantly attributable to a higher risk of ICH. Thus, the proportion of ICH in total hemorrhagic stroke may be a determinant of the relationship between blood pressure and hemorrhagic stroke risk.

The strong association between hypertension and ICH can be supported by plenty of evidence. Hypertension is the most important and prevalent risk factor for spontaneous ICH.^{18–23} Hypertension increases the risk of ICH, particularly in persons who are not compliant with antihypertensive medication, are ≤ 55 years of age, or are smokers.^{19,24} Improved control of hypertension leads to marked reduction in ICH but moderate reduction in ischemic stroke and ischemic heart disease.^{19,25–27} The North American Symptomatic Carotid Endarterectomy Trial (NASCET) observed a great reduction of ICH risk in patients with moderate carotid artery stenosis after strenuous blood pressure control.²⁵ Typically, ICH originates from the spontaneous rupture of small vessels damaged by chronic hypertension. The hypertensive small vessel diseases are characterized by fibrinoid necrosis, hyaline degeneration, microaneurysm formation, and focal hemorrhage, which result from high blood pressure. ICH attributed to hypertension characteristically occurs in the basal ganglia, thalamus, pons, and cerebellum. One hypothesis for why ICH occurs in these locations is that the walls of the lenticulostriate and paramedian vessels that supply these regions are thinner than similar-sized cortical vessels. In addition, the lenticulostriate and paramedian vessels originate directly from main trunk vessel, and they are subject to higher intravascular pressures.^{19–22,25–29}

The deep regions of the brain, where ICH frequently occurs, are also vulnerable to lacunar infarction. Indeed, the same pathology may underlie hypertensive ICH and lacunar infarction, and both types of lesions may be found in the same patient simultaneously.^{20,29–30} Lacunar infarctions may similarly be associated more strongly with hypertension. However, we could not distinguish lacunar infarctions from other ischemic strokes because a database for computed tomography (CT) and MRI reports was not available. We need further

studies on the association between blood pressure and lacunar infarctions.

The present study involved a large sample size (159 705 people) and substantial follow-up (10 years), and the study population showed a relatively high incidence of hemorrhagic stroke. Because of these advantages, we were able to investigate the relationship between a wide range of blood pressures and the risk of stroke subtypes and provide data for men and women separately. Our study also has strength with respect to its generalizability because cohort members were recruited from the general population nationwide. To assess the generalizability of our results to the entire Korean population, we compared characteristics of our participants with corresponding data from the 1998 Korean National Health and Nutrition Examination Survey. The populations were similar for important health indices such as blood pressure, total cholesterol, body mass index, smoking status, and alcohol intake.³¹ The KMIC cohort members were employed workers and might be healthier than the general population in Korea. Although incidence rates of stroke may differ by socioeconomic status, it is still unlikely that the blood pressure–disease relationships should be markedly different.

Our study also has several limitations. First, we had no objective information on the medical histories of the study population. Thus, we excluded people who indicated that they had any previously diagnosed diseases. Second, blood pressure measurement was not standardized well because the health examinations were performed at 416 hospitals nationwide. Thus, blood pressure levels in this study were vulnerable to intraobserver and interobserver error. However, this study involved repeated measurements of exposure variables over 2-year period, and it should have reduced the likelihood of measurement error. Thirdly, KMIC individuals were relatively young (35 to 59 years of age) at baseline. The relationship between risk factors and hemorrhagic stroke may differ by age group,^{4,32} and it needs to be further studied in older age groups. Finally, we could not verify the diagnosis from the hospitalization and death certificate data. In Korea, CT and MRI are routinely used in diagnosis of stroke, and a radiologist's reading is required for insurance claims. According to a nationwide survey of 152 representative hospitals, CT or MRI were used for 89% of the hospital admissions for stroke in 2000.³³ Thus, the validity of diagnosis for stroke from the hospitalization data should be relatively high.

Perspectives

The present study shows that ICH is more closely related with blood pressure than SAH and ischemic stroke in Korean men and women, and that the blood pressure–associated risk of ICH and SAH may differ by sex. Our data suggest that the association between blood pressure and hemorrhagic stroke may be dependent on the relative frequency of ICH and SAH in total hemorrhagic strokes. Our data also emphasize the importance of blood pressure control for the prevention of stroke, especially in countries with a high incidence of ICH.

Acknowledgments

This study was supported in part by Yonsei University Research Fund of 2004, and by a grant of the Korea Health 21 R&D Project,

Ministry of Health and Welfare, Republic of Korea (0412-CR02-0704-0001). We thank the National Health Insurance Corporation for providing the data.

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