Blood Pressure, Proteinuria and Risk of Stroke:

Korea Medical Insurance Corporation Study

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Blood Pressure, Proteinuria and Risk of Stroke:

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ABSTRACT

Objective: To investigate the difference between the risk of stroke according to blood pressure level in people with and without proteinuria.

Methods: Blood pressure, urine protein, and other cardiovascular risk factors were measured in 102,672 Korean men and 60,443 Korean women aged 35 to 59 years in 1990 and 1992. Blood pressure level was classified as non-hypertensive, stage 1 and stage 2 hypertension, and it was based on JNC-7 classification. Proteinuria positive was defined as a dipstick finding of 1+ or greater in either of the 1990 and the 1992 examinations. The principal outcome variables were morbidity and mortality from (1) intracerebral hemorrhage (*International Classification of Disease 10th revision* [ICD-10] codes I61); (2) subarachnoid hemorrhage (ICD-10 codes I60); and (3) ischemic stroke (ICD-10 codes I63, I65 and I66) in an 11 year follow-up from 1993 to 2003.

Results: In baseline examination, proteinuria positive was detected in 1,813 (1.77%) men. 22,179 (21.60%) men had stage 1 hypertension and 6,459 (6.29%) men had stage 2 hypertension. During the follow-up period, there were 554 cases of intracerebral hemorrhage, 152 cases of subarachnoid hemorrhage, and 1978 cases of ischemic stroke. In men, the multivariate-adjusted relative risks (95% confidence interval) of proteinuria positive was 2.60 (1.71-3.94) for intracerebral hemorrhage, 0.44 (0.06-3.21) for subarachnoid hemorrhage and 1.16 (0.89-1.52) for ischemic stroke. The relative risks of stage 2 hypertension were 4.20 (3.15-5.61) for intracerebral hemorrhage, 1.60 (0.98-2.45) for subarachnoid

hemorrhage and 1.26 (1.10-1.46) for ischemic stroke. In men with proteinuria negative, the relative risks of stage 2 hypertension were 1.54 (0.90-2.65) for intracerebral hemorrhage, 0.96 (0.33-2.75) for subarachnoid hemorrhage, and 0.86 (0.66-1.11) for ischemic stroke. In men with proteinuria positive, the relative risks of stage 2 hypertension were 45.03 (3.85-526.41) for intracerebral hemorrhage, 0.96 (0.33-2.75) for subarachnoid hemorrhage, and 0.39 (0.11-1.40) for ischemic stroke. The systolic blood pressure with the largest area under curve (AUC) value of receiver operating characteristic (ROC) analysis to predict intracerebral hemorrhage was 140 mmHg in men with proteinuria negative and 135mmHg in men with proteinuria positive.

Conclusion: In men with proteinuria, the risk of hypertension for intracerebral hemorrhage significantly increased, compared to the risk of hypertension for intracerebral hemorrhage in men without proteinuria. From the results of this study, it could be suggested that early screening and appropriate management of both hypertension and proteinuria can be helpful to prevent intracerebral hemorrhage.

Key words: Proteinuria, hypertension, intracerebral hemorrhage

1. INTRODUCTION

Hypertension is considered the strongest risk factor for stroke. Therefore, management of blood pressure under a certain level is important in preventing strokes. (*Cosentino et al, 2005; Song et al, 2004*)

There have been studies that reported the increased risk of stroke in people with proteinuria. (*McCullough et al, 2007; Madison et al, 2006; Kasper et al, 2005; Tanihara et al, 2005; Yuyun et al, 2004; Roest et al, 2001; Makino et al, 2000; Beamer et al, 1999; Guerrero-Romero et al, 1999; Lin et al, 1984*) Therefore, blood pressure control for people with proteinria is known as important to prevent stroke. The JNC-7 report recommended special considerations, a strict blood pressure target of 130/80 mmHg for people with diabetes or chronic kidney disease patients. This target is lower than the 140/90 mmHg target in other situations. (*Chobanian et al, 2003*)

There are some studies that investigated the combined effect of multiple risk factors (blood pressure, total cholesterol, blood glucose level) on the risk of cardiovascular disease. However, few studies have investigated how blood pressure level affects the risk of stroke in people by the presence of proteinuria. Most studies on the association between proteinuria and the risk of stroke were performed in western countries and focused on ischemic stroke. (*Madison et al, 2006; Yuyun et al, 2004; Roest et al, 2001; Beamer et al, 1999; Guerrero-Romero et al, 1999*) Studies in Japan reported the inconsistent risk of proteinuria and stroke subtype. (*Makino et al, 2000, Lin et al, 1984, Kagan et al, 1985*)

These studies did not show comparison of risks among stroke subtypes because of short follow-up periods and insufficient cases in each stroke subtype.

This study investigated the difference between the risk of stroke according to blood pressure level in people with and without proteinuria in a cohort of 11 years of follow-up.

2. OBJECTIVE

To investigate the difference between the risk of stroke according to blood pressure level in people with and without proteinuria in a cohort of 11 years of follow-up.

3. METHODS

Study Population

The Korea Medical Insurance Corporation (KMIC) study is a cohort study of 172,584 people that is designed to assess the risk factors for chronic diseases. Of the entire South Korean population, which was approximately 43 million in 1990, 4,603,361 (10.7 %) were insured by KMIC, including 1,213,594 workers and their 3,389,767 dependents. KMIC covered civil servants, private teachers, and their dependents. All insured workers were required to participate in biennial medical examinations performed by KMIC. In 1990 and 1992, 94.5 % and 94.4 %, respectively, completed biennial examinations. The cohort in the KMIC study is a systematic, random sample of 108,464 men and 64,120 women, aged 35-59 years.

Of the 172,584 persons, 9,469 (5.5 %) persons were excluded because of incomplete data at baseline for proteinuria, systolic blood pressure, diastolic blood pressure or any of the cardiovascular risk factors studied (serum cholesterol concentration, fasting blood glucose concentration, body mass index, and smoking status), or people that reported one or more previously diagnosed diseases. This resulted in a final sample size of 163,115 persons: 102,672 men and 60,443 women.

Data Collection

Baseline information was obtained from health examinations in 1990 and 1992. Averages of the two measurements taken during these examinations were used. The examinations were conducted in a standardized manner by trained medical staff at 416 hospitals nationwide.

The participants' weight, height, and blood pressure were measured at each examination. Fasting blood specimens were analyzed by automated instruments at each hospital for total cholesterol, glucose, and hemoglobin concentration. Fasting blood specimens were analyzed by automated instruments at each hospital for total cholesterol, glucose, and hemoglobin concentration. Each hospital that participated in the health assessment followed the internal and external quality control procedures stipulated by the Korean Society of Quality Control in Clinical Pathology. (*Min et al, 2001*)

Systolic and diastolic blood pressure was measured in the seated position with a mercury sphygmomanometer or automatic manometer. They were divided into three groups of blood pressure level; non-hypertensive (systolic blood pressure < 140mmHg and diastolic blood pressure < 90mmHg); stage 1 hypertension (140 to 159/90 to 99 mm Hg); stage 2 hypertension (>=160/>=100 mm Hg). When systolic and diastolic blood pressures fell into different categories, the higher category was selected. (*Chobanian et al, 2003*)

Urine protein concentration was determined by a urine dipstick semi-quantitative analysis (N-multistix; Ames Division of Miles Laboratory Inc,

Elkhart, Ind). The results of the urine test were based on a color scale that quantified proteinuria as absent, trace, 1+, 2+, 3+, and 4+. Dipstick results of trace, 1+, and 2+ corresponded to protein concentrations of about 0.1, 0.3, and 1.0 g/L, respectively. Reported specificity was 97.4 % and sensitivity was 46.0 %. (*Atkins et al, 2003 Pugia et al, 2001*) Proteinuria status was defined as positive (with proteinuria) or negative (without proteinuria); proteinuria positive was defined as dipstick finding of 1+ or greater in either of the 1990 and 1992 examinations.

The principal outcome variables were morbidity and mortality from (1) intracerebral hemorrhage (*International Classification of Disease 10th revision* [ICD-10] codes I61); (2) subarachnoid hemorrhage (ICD-10 codes I60); and (3) ischemic stroke (ICD-10 codes I63, I65 and I66). The follow-up period was 11 years, from 1993 to 2003. For individuals who had more than one event, only the first event was used in analyses. Non-fatal outcomes were ascertained from health insurance claim data and fatal outcomes from death certification data.

Statistical Analysis

Men and women were studied separately. The categories for fasting glucose concentrations was < 100.0, 100.0 to 126.0, and ≥126.0 mg/dL. The categories for serum cholesterol concentrations were <200.0, 200.0 to 240.0, and ≥240.0 mg/dL. Smoking status categories included current smokers, ex-smokers, and nonsmokers. Based on the average daily alcohol intake, participants were classified as non-drinkers, moderate drinkers (<50g/d), or heavy drinkers (>=50g/d). In respective proteinuria status, subjects were divided into blood pressure level: non-hypertensive, stage 1 and stage 2 hypertension.

To calculate relative risk, Cox's proportional-hazards models were used in each subgroup of blood pressure level and proteinuria after adjustment for the aforementioned variables. For all relative risks, 95 % confidence intervals were calculated.

To evaluate predictability for stroke in subjects with specific blood pressure level in respective proteinuria status, receiver operating characteristic (ROC) analysis was performed. The results of ROC analysis described sensitivity, specificity, and area under curve (AUC). The AUC on specific systolic blood pressure level, which was adjusted for variables used in calculating relative risk, is considered to be a cut-off value for detecting strokes.

4. RESULTS

Baseline Characteristics of the Study Population

Table 1 shows the baseline characteristics of the study population. The mean age was 44.92 years old for men and 42.42 years old for women. Proportions of hypertension were 27.89 % in men and 10.46 % in women. Proteinuria positive was detected in 1,813 men (1.77 %) and 600 women (0.99 %).

Table 1. Baseline Characteristics of Study Population

Characteristic	Men N=102,672		Women N=60,443	
Age, years	44.92	± 6.66	42.42	± 6.67
Body mass index, Kg/m^2	23.47	± 2.40	23.32	± 2.48
Total serum cholesterol, mg/dL	194.25	± 32.95	189.37	± 32.45
Fasting serum glucose, mg/dL	92.30	± 18.37	86.09	± 11.70
Blood pressure level				
Non-hypertensive	74,034	(72.11)	54,120	(89.54)
Stage 1 hypertension	22,179	(21.60)	5,061	(8.37)
Stage 2 hypertension	6,459	(6.29)	1,262	(2.09)
Proteinuria status				
Negative	100,859	(98.23)	59,843	(99.01)
Positive*	1,813	(1.77)	600	(0.99)
Alcohol intake, g/day				
<50	93,196	(90.77)	59,304	(98.12)
≥50	9,476	(9.23)	1,139	(1.88)
Smoking status				
Non-smoker	20,973	(21.30)	49,017	(99.15)
Ex-smoker	20,365	(20.68)	220	(0.45)
Current smoker	57,133	(58.02)	198	(0.40)

Data is presented as mean ± SD or No.(%).

* Defined as at least 1+ or greater of dipstick finding in 1990 and 1992 examination.

Baseline Characteristics of the Study Population according to Blood Pressure Level in Respective Proteinuria Status

Table 2 shows the baseline characteristics of the study population according to blood pressure level in respective proteinuria status. Body mass index, total serum cholesterol, and fasting serum glucose level increased from the left to the right of the table. (p-value for trend <0.001).

At the same level of blood pressure, these values were higher in men and women with proteinuria positive. The proportion of subjects who drank more than 50g alcohol a day and current smokers did not show this trend.

Table 2. Baseline Characteristics according to Blood Pressure Level in Respective Proteinuria Status

Characteristics	Proteinuria negative			Proteinuria positive*			p-value for trend
	Non-hypertensive	Stage1 hypertension	Stage2 hypertension	Non-hypertensive	Stage1 hypertension	Stage2 Hypertension	
Men, N=102,672	**N=73,132**	**N=21,615**	**N=6,112**	**N=902**	**N=564**	**N=347**	
Age, years	44.04± 6.50	46.75± 6.63	48.63± 6.14	44.97± 6.54	46.87± 6.39	47.93± 5.94	<0.001
Body mass index, Kg/m^2	23.17± 2.32	24.11± 2.40	24.44± 2.49	23.78± 2.62	24.77± 2.64	25.24± 2.88	<0.001
Total serum cholesterol, mg/dL	191.73±31.80	199.26±34.04	202.26±35.88	203.79±38.33	206.85±39.18	212.99±45.90	<0.001
Fasting serum glucose, mg/dL	90.66±16.32	95.36±20.75	98.31±23.55	96.19±27.77	102.75±29.73	105.28±32.23	<0.001
% of alcohol drinker ≥50g/day	6,236 (8.53)	2,287 (10.58)	739 (12.09)	89 (9.87)	82 (14.54)	43 (12.39)	<0.001
% of current smokers	41,794 (59.52)	11,371 (54.83)	2,999 (51.79)	512 (60.09)	288 (53.73)	169 (50.75)	<0.001
Women, N=60,443	**N=53,666**	**N=4970**	**N=1207**	**N=454**	**N=91**	**N=55**	
Age, years	41.83± 5.88	47.05± 6.49	49.41± 5.85	42.35± 5.74	46.21± 6.30	47.16± 6.26	<0.001
Body mass index, Kg/m^2	22.12± 2.37	23.81± 2.71	24.55± 2.86	22.57± 2.85	24.52± 2.94	24.77± 3.65	<0.001
Total serum cholesterol, mg/dL	187.57±31.60	203.23±34.89	208.69±36.43	191.69±33.30	209.71±41.91	216.69±43.80	<0.001
Fasting serum glucose, mg/dL	85.52±10.78	89.90±14.45	93.42±20.28	88.74±20.99	95.93±28.27	98.96±30.67	<0.001
% of alcohol drinker ≥50g/day	990 (1.84)	117 (2.35)	24 (1.99)	95 (7.01)	84 (12.82)	43 (10.70)	0.138
% of current smokers	161 (0.36)	27 (0.70)	8 (0.89)	6 (2.20)	2 (2.20)	0 (0.00)	0.007

Data are presented as mean ± SD or No.(%).

* Defined as at least 1+ or greater of dipstick finding in 1990 and 1992 examination.

Number of Events and Incidence of Stroke according to Blood Pressure Level in Respective Proteinuria Status

Table 3 shows the number of events and incidence of stroke according to blood pressure level in respective proteinuria status.

During 11 years of study, the men have had 554 cases of intracerebral hemorrhage, 152 cases of subarachnoid hemorrhage, and 1978 cases of ischemic stroke. For the women in the same period, there have been 100 cases of intracerebral hemorrhage, 67 cases of subarachnoid hemorrhage, and 570 cases of ischemic stroke.

The incidence per 100,000 person-years of intracerebral hemorrhage and ischemic stroke increased according to blood pressure level and proteinuria status (from the left to the right of the table) in both men and women. The number of cases of intracerebral hemorrhage was smaller than ischemic stroke. The incidence of intracerebral hemorrhage per 100,000 person-years was greater than that of ischemic stroke.

Table 3. Number of Events and Incidence of Stroke according to Blood Pressure Level in Respective Proteinuria Status

Stroke subtype	No. of events (Incidence per 100000 person-years)													
	Total		Proteinuria negative						Proteinuria positive*					
			Non-Hypertensive		Stage1 Hypertension		Stage2 Hypertension		Non-hypertensive		Stage1 Hypertension		Stage2 hypertension	
Men, N=102,672	**N=102,672**		**N=73,132**		**N=21,615**		**N=6,112**		**N=902**		**N=564**		**N=347**	
Total Stroke	2,696	(240.9)	1,231	(165.6)	875	(329.6)	478	(636.9)	25	(259.9)	47	(730.6)	40	(1,098.8)
Intracerebral hemorrhage	554	(49.2)	200	(26.3)	167	(65.0)	143	(225.9)	6	(62.2)	17	(297.1)	21	(731.4)
Subarachnoid hemorrhage	152	(13.5)	77	(9.7)	53	(21.3)	20	(32.5)	1	(9.9)	1	(8.8)	0	(N/A)
Ischemic stroke	1,978	(173.4)	938	(127.0)	658	(242.9)	315	(389.8)	18	(185.2)	30	(427.3)	19	(427.3)
Women, N=60,443	**N=60,443**		**N=53,666**		**N=4,970**		**N=1,207**		**N=454**		**N=91**		**N=55**	
Total Stroke	749	(113.0)	510	(93.9)	164	(214.3)	64	(487.5)	6	(114.3)	1	(43.8)	4	(471.3)
Intracerebral hemorrhage	100	(5.2)	55	(10.0)	30	(48.0)	12	(117.7)	2	(34.0)	0	(N/A)	1	(73.8)
Subarachnoid hemorrhage	67	(3.5)	48	(8.6)	12	(27.3)	7	(39.6)	0	(N/A)	0	(N/A)	0	(N/A)
Ischemic stroke	570	(27.9)	400	(73.8)	118	(130.4)	43	(325.5)	4	(129.4)	1	(43.8)	4	(471.3)

* Defined as at least 1+ or greater of dipstick finding in 1990 and 1992 examination.

Relative Risks of Stroke according to Blood Pressure Level and Proteinuria Status

Table 4 shows relative risks of stroke according to blood pressure level and proteinuria status. The multivariate-adjusted relative risks (95 % confidence interval) of proteinuria positive were 2.60 (1.71-3.94) for intracerebral hemorrhage, 0.44 (0.06-3.21) for subarachnoid hemorrhage, and 1.16 (0.89-1.52) for ischemic stroke. The relative risks of stage 1 hypertension were 2.35 (1.82-3.05) for intracerebral hemorrhage, 1.92 (1.25-2.96) for subarachnoid hemorrhage, and 1.29 (1.16-1.44) for ischemic stroke. The relative risks of stage 2 hypertension were 4.20 (3.15-5.61) for intracerebral hemorrhage, 1.60 (0.98-2.45) for subarachnoid hemorrhage, and 1.26 (1.10-1.46) for ischemic stroke. Proteinuria positive was significantly associated with intracerebral hemorrhage.

In women, the multivariate-adjusted relative risks of proteinuria positive were 2.60 (1.71-3.94) for ischemic stroke, but were not assessable for subarachnoid and intracerebral hemorrhage. The relative risks of stage 1 hypertension were 3.45 (1.80-6.60) for intracerebral hemorrhage, 0.81 (0.30-2.19) for subarachnoid hemorrhage and 1.09 (0.84-1.42) for ischemic stroke. The relative risks of stage 2 hypertension were 3.59 (1.36-9.47) for intracerebral hemorrhage, 1.61 (0.46-5.63) for subarachnoid hemorrhage, and 1.22 (0.84-1.78) for ischemic stroke. Hypertension was associated with the risk of intracerebral hemorrhage, while proteinuria positive was not significantly associated with the risk of any stroke subtype.

Table 4. Relative Risks of Stroke according to Blood Pressure Level and Proteinuria Status

Characteristics	RR (95 % CI) †			
	Total stroke	Intracerebral hemorrhage	Subarachnoid hemorrhage	Ischemic stroke
Men, N=102,672				
No. of cases (Incidence per 100000 person year)	2,696 (241.0)	554 (49.2)	152 (13.5)	1,978 (173.4)
Blood pressure level				
Non-hypertensive	1.00	1.00	1.00	1.00
Stage 1 hypertension	1.40 (1.27-1.54)	2.35 (1.82-3.05)	1.92 (1.25-2.96)	1.29 (1.16-1.44)
Stage 2 hypertension	1.53 (1.35-1.73)	4.20 (3.15-5.61)	1.60 (0.98-2.45)	1.26 (1.10-1.46)
Proteinuria status				
Negative	1.00	1.00	1.00	1.00
Positive*	1.35 (1.08-1.70)	2.60 (1.71-3.94)	0.44 (0.06-3.21)	1.16 (0.89-1.52)
Women, N=60,443				
No. of cases (Incidence per 100000 person year)	749 (113.0)	100 (5.2)	67 (3.5)	570 (27.9)
Blood pressure level				
Non-hypertensive	1.00	1.00	1.00	1.00
Stage 1 hypertension	1.25 (0.99-1.58)	3.45 (1.80-6.60)	0.81 (0.30-2.19)	1.09 (0.84-1.42)
Stage 2 hypertension	1.38 (0.99-1.81)	3.59 (1.36-9.47)	1.61 (0.46-5.63)	1.22 (0.84-1.78)
Proteinuria status				
Negative	1.00	1.00	1.00	1.00
Positive*	0.74 (0.30-1.81)	N/A	N/A	0.90 (0.36-2.20)

†Adjusted for age, sex, smoking status, amount of alcohol intake, body mass index, blood pressure level, fasting serum glucose, and total serum cholesterol levels, and proteinuria.

* Defined as at least 1+ or greater of dipstick finding in 1990 and 1992 examination.

Relative Risks for Stroke according to Blood Pressure Level in Respective Proteinuria Status

Table 5 shows the risks for stroke according to blood pressure level in respective proteinuria status. For men in both proteinuria statuses, the non-hypertensive level of blood pressure was used as a reference category. The risk of intracerebral hemorrhage increased as the level of blood pressure went up. The amount of increase was greater in men with proteinuria positive than in men with proteinuria negative. The risk of subarachnoid hemorrhage and ischemic stroke did not increase. The risk of intracerebral hemorrhage increased even after additional adjustment for systolic blood pressure as a continuous variable.

The risks of stroke in women with proteinuria at baseline were not assessable because of a small number or absence of events. The significance of the risk of intracerebral hemorrhage in women with proteinuria negative changed after additional adjustment for systolic blood pressure as a continuous variable.

Table 5. Relative Risks of Stroke according to Blood Pressure Level in Respective Proteinuria Status

Proteinuria status	Blood pressure level	Intracerebral hemorrhage		Subarachnoid hemorrhage		Ischemic stroke	
		RR (95 % CI)[A]	RR (95 % CI)[B]	RR (95 % CI)[A]	RR (95 % CI)[B]	RR (95 % CI)[A]	RR (95 % CI)[B]
Men, N=102,672							
Negative	**Non-hypertensive**	1.00	1.00	1.00	1.00	1.00	1.00
Negative	**Stage 1 hypertension**	2.19 (1.68-2.86)	1.48 (1.07-2.03)	1.96 (1.27-3.02)	1.53 (0.87-2.68)	1.30 (1.16-1.45)	1.09 (0.95-1.26)
Negative	**Stage 2 hypertension**	3.92 (2.91-5.29)	1.54 (0.90-2.65)	1.70 (0.91-3.17)	0.96 (0.33-2.75)	1.27 (1.10-1.47)	0.86 (0.66-1.11)
Positive*	**Non-hypertensive**	1.00	1.00	1.00	1.00	1.00	1.00
Positive*	**Stage 1 hypertension**	18.77 (2.40-146.95)	22.74 (2.62-197.67)	N/A	N/A	1.00 (0.51-1.98)	0.73 (0.32-1.64)
Positive*	**Stage 2 hypertension**	30.48 (3.85-241.71)	45.03 (3.85-526.41)	N/A	N/A	0.79 (0.36-1.71)	0.39 (0.11-1.40)
Women, N=60,443							
Negative	**Non-hypertensive**	1.00	1.00	1.00	1.00	1.00	1.00
Negative	**Stage 1 hypertension**	3.45 (1.80-6.60)	2.11 (0.86-5.20)	0.81 (0.30-2.19)	0.35 (0.10-1.16)	1.11 (0.85-1.44)	1.11 (0.79-1.57)
Negative	**Stage 2 hypertension**	3.59 (1.36-9.47)	1.41 (0.30-6.66)	1.61 (0.46-5.63)	0.29 (0.04-2.02)	1.25 (0.86-1.83)	1.27 (0.73-2.21)
Positive*	**Non-hypertensive**	1.00	1.00	1.00	1.00	1.00	1.00
Positive*	**Stage 1 hypertension**	N/A	N/A	N/A	N/A	N/A	N/A
Positive*	**Stage 2 hypertension**	N/A	N/A	N/A	N/A	N/A	N/A

A: Adjusted for age, sex, smoking status, amount of alcohol intake, body mass index, fasting serum glucose, and total serum cholesterol levels.
B: Adjusted for variables mentioned in A and systolic blood pressure as a continuous variable.
* Defined as at least 1+ or greater of dipstick finding in 1990 and 1992 examination.

Receiver Operating Characteristic (ROC) Analysis of Systolic Blood Pressure for Identification of Men at Risk of Intracerebral Hemorrhage in Respective Proteinuria Status

Table 6 shows the result of receiver operating characteristic (ROC) analysis of systolic blood pressure for identification of men at risk of intracerebral hemorrhage in respective proteinuria status. The systolic blood pressure with largest area under curve (AUC) value was 140 mmHg in men with proteinuria negative and 135mmHg in men with proteinuria positive. In systolic blood pressure 135mmHg, the difference between the AUC values in respective proteinuria status was statistically significant.

Table 6. Results of Receiver Operating Characteristic (ROC) Analysis of Systolic Blood Pressure for Identification of Men at Risk of Intracerebral Hemorrhage in Respective Proteinuria Status

Systolic blood pressure, mmHg	Proteinuria negative			Proteinuria positive*			P-value
	Sensitivity	Specificity	AUC†	Sensitivity	Specificity	AUC†	
95	1.00	0.00	0.647	1.00	0.00	0.646	0.942
100	1.00	0.00	0.648	1.00	0.01	0.648	0.942
105	0.99	0.05	0.653	1.00	0.03	0.650	0.942
110	0.98	0.12	0.661	1.00	0.07	0.649	0.965
115	0.93	0.26	0.670	0.98	0.14	0.676	0.661
120	0.86	0.42	0.681	0.98	0.24	0.715	0.254
125	0.78	0.59	0.714	0.92	0.36	0.723	0.482
130	0.68	0.71	0.728	0.89	0.49	0.770	0.067
135	0.56	0.81	0.731	0.85	0.60	0.789	0.045
140	0.47	0.88	0.732	0.75	0.69	0.785	0.207
145	0.33	0.92	0.711	0.57	0.78	0.746	0.375
150	0.26	0.95	0.708	0.40	0.83	0.707	0.832

† AUC: Area under curve, adjusted for age, sex, smoking status, amount of alcohol intake, body mass index, fasting serum glucose, and total serum cholesterol levels.
* Defined as at least 1+ or greater of dipstick finding in 1990 and 1992 examination.

5. DISCUSSION

The main results of this study show that the risk of intracerebral hemorrhage in hypertensive men with proteinuria positive greatly increased compared to the men with proteinuria negative. The risk of ischemic stroke or subarachnoid hemorrhage in men with proteinuria positive did not increase significantly.

Blood Pressure, Proteinuria and Risk of Stroke

This study show that the risk of intracerebral hemorrhage in hypertensive men with proteinuria positive increased greatly. As it is expected, hypertension was prevalent in subjects with proteinuria positive. Calculated from Table 3, men with proteinuria positive had a 50.2 % prevalence of hypertension, whereas only 27.5 % of men with proteinuria negative had hypertension. For women, 24.3 % with proteinuria positive had hypertension and only 10.3 % of women that had proteinuria negative had hypertension. The risk assessment based on blood pressure level and proteinuria status seems appropriate to implement preventive interventions, which could emphasize the early screening and intensive control of hypertension and proteinuria, using such drugs as angiotensin converting enzyme (ACE) inhibitors or angiotensin antagonist. These drugs are known effective for blood pressure control and proteinuria reduction. (*Ibrahim et al, 2006; Consentino et al, 2001*)

The significant association between proteinuria, hypertension and

intracerebral hemorrhage in women was not observed in this study. Some previous studies mentioned lower or insignificant risk of proteinuria for the risk of stroke in women. (*Jee et al, 2005; Tsioufis et al, 2004; Roest et al, 2001*) This result could be due to the small number of women profiled and the relatively healthier risk factor profiles of women. (Table 1, 4)

In this population study, the blood pressure categories were used to describe the impact of high blood pressure on the risk of stroke in men with proteinuria positive. To evaluate the predictability of intracerebral hemorrhage in specific blood pressure levels in respective proteinuria status, receiver operating characteristic (ROC) analysis was performed for men. The results of ROC analysis showed that systolic blood pressure level 135mmHg in men with proteinuria positive is highest in predicting intracerebral hemorrhage during 11 years. (Table 6) Considering the upward shift of systolic blood pressure in men with proteinuria positive,(Table 2) it could be suggested that lower value (under 135mmHg) of systolic blood pressure in men with proteinuria positive, as a cut-off level in order to detect subjects at risk of intracerebral hemorrhage. In further analysis, cut-point of the JNC-7 report, targeting baseline blood pressure levels as 130/80mmHg in people with diabetes or chronic kidney disease was used. For men with proteinuria positive, there were 43 out of 44 events of intracerebral hemorrhage in men with baseline blood pressure levels above 130/80 mmHg. (Appendix table 1) When the cut-point was changed into baseline blood pressure level 120/80 mmHg (Normal category of JNC-7 classification), there were all (44 out of 44) events of intracerebral hemorrhage in men with baseline blood

pressure level above 120/80 mmHg in men with proteinuria positive. (Appendix table 2) Thus, it could be concluded that the result from this study strongly support JNC-7 recommendation targeting blood pressure level as 130/80 mmHg, in men with proteinuria positive.

Possible Explanations

A simple multiplication of relative risks from Table 4 for intracerebral hemorrhage in men with proteinuria positive and stage 1 hypertension is 6.11, yet in this study, it was found that relative risk of intracerebral hemorrhage for men with the same conditions to be 18.77. The gap increased greater for people with proteinuria positive and stage 2 hypertension (10.9 to 30.5). Thus, the risk is not merely explained by a simple additive or multiplicative effect of two risk factors. Explanation on a synergistic effect of hypertension and proteinuria on the risk of intracerebral hemorrhage can be proposed.

First, endothelial dysfunction might aggravate the risk of intracerebral hemorrhage in hypertensive subjects. Intracerebral hemorrhage is known as the most sensitive stroke subtype to hypertension. (*Cosentino et al, 2005; Song et al, 2004*) In men with hypertension, proteinuria might play a role in increasing risk of intracerebral hemorrhage in this study. Proteinuria is caused by increased permeability of an injured endothelium. An injured endothelium results in increased adhesiveness, decreased nitric oxide release, altered production of vaso-active mediators, and most importantly, atherosclerosis. (*Tsioufis et al,*

2004; Paisley et al, 2003; Consentino et al, 2001) These findings point out that proteinuria could be a marker of early intravascular destruction. (*Paisley et al, 2003*) An injured endothelium does not respond to elevated blood pressure or anti-hypertensive, which could lead to cardiovascular accidents. (*Ibrahim et al, 2006; Consentino et al, 2001; Samuelsson et al, 1985*) Thus, it could be summarized that the interaction between higher blood pressure level and an injured endothelium might lead to intracerebral hemorrhage.

Second, the increased risk of intracerebral hemorrhage, rather than ischemic stroke or subarachnoid hemorrhage, might be due to increased hemorrhagic tendency in men with protineuria. In previous studies that reported on the positive association between proteinuria and stroke, most of the research on ischemic stroke did not include intracerebral hemorrhage, which was not prevalent in western countries. Studies in Japan reported stronger association between proteinuria and ischemic stroke than intracerebral hemorrhage, which was quite different from the results of this study. As mentioned above, the result of this study was partly explained by a strong association between intracerebral hemorrhage and high blood pressure levels. In this study, the risk of intracerebral hemorrhage in men with proteinuria positive was higher even after the additional adjustment for blood pressure level, whereas, the risks of subarachnoid hemorrhage and ischemic stroke were not significantly increased in men with both hypertension and proteinuria positive. Increased hemorrhagic tendency in people with proteinuria has been reported. In some studies, proteinuria is known to represent the duration and severity of hypertension, with underlying arterial

remodeling and loss of distensibility. Arterial remodeling could lead to the rupture and hemorrhage of blood vessels. (*Stennett et al, 2006;; Lin et al, 1984*) ACE inhibitors, which are known to prevent arterial remodeling, is reported to cause both endothelium recovery and proteinuria reduction in some studies. Some common mechanisms related to proteinuria and vascular remodeling was suggested. (*Rossi et al, 1995*) The close association between proteinuria and hemorrhagic stroke has been recognized in many case reports of hemorrhagic stroke in preeclampsia. In preeclampsia, vascular reactivity and activation of coagulation cascade, which lead to cerebral hemorrhage. (*Granger et al, 2001; Pridjian et al, 2002; Stennett et al, 2006*) Thus, it could be summarized that increased hemorrhagic tendency in proteinuria might lead to intracerebral hemorrhage.

The smaller risk of ischemic stroke may be due to a relatively younger age distribution of this study population. Ischemic stroke is largely from carotid artery atherosclerosis and thrombus from cardiac origin. From previous studies, atherosclerosis progressed with age and the risk significantly increased in men aged 45 years and older and in women aged 55 years and older. (*Kasper et al, 2005)* In this study the mean age was 44.92 years for men and 42.42 for women. (Table 1) Further analysis was performed on the risk of ischemic stroke according to blood pressure level in different age groups. The risk of ischemic stroke in men aged 45 years and older was not significantly higher than in men aged less than 45 years. (Appendix table 3)

Third, there is a possibility of confounding variables of blood pressure,

which was categorized as 3 categorical variables. However, systolic blood pressure as a continuous variable was adjusted and the risk did not change significantly after adjustment.

Strengths and Limitations

This study has several important strengths. First, this study had a large sample size (102,672 men and 60,443 women) and a long follow-up period (11 years). Most previous studies on stroke investigated ischemic stroke or had a short follow-up period. This study included enough sample sizes and follow-up period for investigating stroke in various subtypes. Second, there were repeatedly measured major independent variables over 2 years; thus, the possibility of measurement errors could be decreased. Third, in this study, proteinuria positive was defined as a dipstick finding of 1+ or greater in both the 1990 and 1992 examination. These methods could improve the sensitivity of detecting proteinuria with high specificity, since measuring dipstick proteinuria is known to have low sensitivity and high specificity. (*Atkins et al, 2003; Pugia et al, 2001*) For all our efforts, the prevalence of proteinuria positive in hypertensive subjects (3.18 % in men and 2.38 % in women) was low compared to previous reports. These findings could alleviate the strength of association in this study.

This study has potential limitations. First, the diagnosis from hospitalization and death certificate data was not verified. Thus, there is some possibility of inaccurate diagnosis and a misclassification bias. However, a misclassification

bias, if any, would likely to cause a reduction of relative risk since the misclassification would mainly be due to unclassified events rather than misdiagnosis. According to Korean nationwide survey data, the use of computerized tomography for stroke was 89 % in 1999 and 2000. Second, with dilute urine specimens, significant proteinuria could be overlooked with dipstick methods because a trace reading from a dipstick method is known to indicate a protein concentration of 1 to 30mg/100mL. (*Atkins et al, 2003*) This level has been reported to be associated with cardiovascular mortality. Thus, misclassification bias, if any, would likely cause a reduction of the relative risk. Third, although adjustment was performed for as many confounding variables as possible, residual confounding might still exist.

6. CONCLUSION

In Korean men with hypertension, the risk for intracerebral hemorrhage significantly increased when proteinuria was detected. This finding was not observed in women. Therefore, it could be concluded that the early screening and aggressive management of both hypertension and proteinuria is important to prevent intracerebral hemorrhage in men.

For early detection and management for people at the risk of intracerebral hemorrhage, health examination using the dipstick method could be emphasized. Intracerebral hemorrhage is prevalent in developing countries. In these countries, detecting proteinuria with the dipstick method and blood pressure measurement could be a cheap and easy way of detecting the at-risk population for intracerebral hemorrhage before using UAER on a specific population thought to have a certain disease.

From the results of this study, it could be suggested that people detected with proteinuria, the blood pressure should be checked and controlled under a level at least 135mmHg and hopefully under 130mmHg. Further medical evaluation on the cause of proteinuria (ex,nephritic syndrome, glomerulonephritis, impaired fasting glucose, diabetes) should be performed. According to the cause of proteinuria, appropriate management of both proteinuria and blood pressure should be performed.

Appendix table 1. Number of Stroke Events according to Blood Pressure Level in Respective Proteinuria Status in Men

Proteinuria status	Systolic blood pressure, mmHg		Diastolic blood pressure, mmHg	Number of stroke events		
				Intracerebral hemorrhage	Subarachnoid hemorrhage	Ischemic stroke
Negative	**<130**	**And**	**80**	65	21	314
Negative	**130-139**	**or**	**80-89**	135	56	624
Negative	**140-159**	**or**	**90-99**	167	53	658
Negative	**≥160**	**or**	**≥100**	143	20	315
Positive*	**<130**	**and**	**<80**	1	1	6
Positive*	**130-139**	**or**	**80-89**	5	0	12
Positive*	**140-159**	**or**	**90-99**	17	1	30
Positive*	**≥160**	**or**	**≥100**	21	0	19

* Defined as at least 1+ or greater of dipstick finding in 1990 and 1992 examination.

Appendix table 2. Number of Stroke Events by Subtype according to JNC-7 Classification of Blood Pressure Level in Respective Proteinuria status in Men

Proteinuria status	Blood pressure level according to JNC-7 classification	Number of stroke events		
		Intracerebral hemorrhage	Subarachnoid hemorrhage	Ischemic stroke
Negative	**Normal**	45	17	234
Negative	**Pre-hypertension**	155	60	704
Negative	**Stage 1 hypertension**	167	53	658
Negative	**Stage 2 hypertension**	143	20	315
Positive*	**Normal**	0	1	3
Positive*	**Pre-hypertension**	6	0	15
Positive*	**Stage 1 hypertension**	17	1	30
Positive*	**Stage 2 hypertension**	21	0	19

* Defined as at least 1+ or greater of dipstick finding in 1990 and 1992 examination.

Appendix table 3. Relative Risks of Ischemic Stroke according to Blood Pressure Level in Respective Proteinuria Status in Men

Proteinuria status	Blood pressure level	RR (95 %CI) of ischemic stroke	
		Age<45 years	Age≥45 years
Negative	**Non-hypertensive**	1.00	1.00
Negative	**Stage 1 hypertension**	1.51 (1.21-1.87)	1.27 (1.12-1.44)
Negative	**Stage 2 hypertension**	1.42 (1.01-1.99)	1.29 (1.10-1.51)
Positive*	**Non-hypertensive**	1.00	1.00
Positive*	**Stage 1 hypertension**	0.24 (0.02-3.20)	0.91 (0.41-2.03)
Positive*	**Stage 2 hypertension**	N/A	0.65 (0.28-1.74)

* Defined as at least 1+ or greater of dipstick finding in 1990 and 1992 examination.

REFERENCES

Atkins RC, Briganti AE, Zimmet PZ, Chadban SJ. Association between albuminuria and proteinuria in the general population: the AusDiab Study. Nephrol Dial Transplant 2003; 18: 2170–2174

Beamer NB, Coull BM, Clark WM, Wynn M. Microalbuminuria in ischemic stroke. *Arch Neurol* 1999; 56: 699-702

Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ; National Heart, Lung, and Blood Institute Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289: 2560-2572

Consentino F, Rubattu S, Savoia C, Venturelli V, Pagannonne E, Volpe M. Endothelial dysfunction and stroke. *J Cardiovasc Pharmacol* 2001: 38: s75-78

Cosentino F, Volpe M. Hypertension, stroke, and endothelium. *Curr Hypertens Rep* 2005; 7: 68-71

Granger JP, Alexander BT, Llinas MT, Bennettt WA, Khalil RA. Pathophysiology of hypertension during preeclampsia linking placental ischemia with endothelial dysfunction *Hypertension* 2001; 38: 718-722

Guerrero-Romero F, Rodriguez-Moran M. Proteinuria is an independent risk factors for ischemic stroke in non-insulin-dependent diabetes mellitus. *Stroke* 1999; 30: 1787-1791

Ibrahim MM. RAS inhibition in hypertension. *J Hum Hypertens* 2006; 20: 101-108

Jee SH, Boulware LE, Guallar E, Suh I, Appel LJ, Miller ER 3rd. Direct, progressive association of cardiovascular risk factors with incident proteinuria: results from the Korea Medical Insurance Corporation (KMIC) study. *Arch Intern Med* 2005; 165: 2299-2304

Kagan A, Popper JS, Rhoads GG, Yano K. Dietary and other risk factors for stroke in Hawaiian Japanese men. *Stroke* 1985; 16: 390-396

Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL. Harrison's Principles of Internal Medicine. 16th edition. McGraw-Hill, New-York, USA 2005

Lin CH, Shimizu Y, Kato H, Robertson TL, Furonaka H, Kodama K, Fukunaga Y. Cerebrovascular disease in a fixed population of Hiroshima and Nagasaki, with special reference to relationship between type and risk factors. *Stroke* 1984; 15: 653-660

McCullough PA, Jurkovitz CT, Pergola PE, McGill JB, Brown WW, Collins AJ, Chen SC, Li S, Singh A, Norris KC, Klag MJ, Bakris GL; for the KEEP Investigators. Independent components of chronic kidney disease as a cardiovascular risk state: results from the Kidney Early Evaluation Program (KEEP). *Arch Intern Med* 2007; 167: 1122-1129

Madison JR, Spies C, Schatz IJ, Masaki K, Chen R, Yano K, Curb JD. Proteinuria and risk for stroke and coronary heart disease during 27 years of follow-up The Honolulu Heart Program. *Arch Intern Med* 2006; 166: 884-889

Makino Y, Kawano Y, Minami J, Yamaguchi T, Takishita S. Risk of stroke in relation to level of blood pressure and other risk factors in treated hypertensive patients. *Stroke* 2000; 31: 48-52

Min WK, Kim YK, Kwon OH, Kim KD, Kim SS, Kim JW, Kim JQ, Kim TJ, Park MR, Ahn KS, Jung NS, Jung HS, Hong KS, Annual report on external quality assessments in clinical chemistry in Korea (2000). *J Clin Pathol Qual* Cont 2001; 23: 1-14

Paisley KE, Beaman M, Tooke JE, Mohamed-Ali V, Lowe GD, Shore AC. Endothelial dysfunction and inflammation in asymptomatic proteinuria. *Kidney Int* 2003; 63: 624-633

Pridjian G, Puschett JB. Preeclampsia. Part 1: Clinical and pathophysiologic considerations. OBSTETRICAL AND GYNECOLOGICAL SURVEY 2002; 57: 598-617

Pugia MJ, Wallace JF, Lott JA, Sommer R, Luke KE, Shihabi ZK, Sheehan M, Bucksa JM. Albuminuria and proteinuria in hospitalized patients as measured by quantitative and dipstick methods. *J Clin Lab Anal* 2001; 15: 295-300

Roest M, Banga JD, Janssen WM, Grobbee DE, Sixma JJ, Jong PE, Zeeuw D, Schouw YT. Excessive urinary albumin levels are associated with future cardiovascular mortality in postmenopausal women *Circulation* 2001; 103: 3057-3061

Rossi G, Rossi A, Sacchetto A, Pavan E, Pessina AC. Hypertensive cerebrovascular disease and the renin-angiotensin system. (review) *Stroke* 1995; 26 :1700-1706

Samuelsson O, Wilhelmsen L, Pennert K, Berglund G. Prognostic factors in treated hypertension. *J Hypertens* 1985; 3: s497-500

Song YM, Sung J, Lawlor DA, Smith GD, Shin Y, Ebrahim S. Blood pressure, haemorrhagic stroke, and ischaemic stroke: the Korean National Prospective Occupational Cohort Study. *BMJ* 2004; 328: 324-325

Stennett AK, Khalil RA. Neurovascular mechanisms of hypertension in pregnancy. Curr Neurovasc Res 2006; 3: 131-148

Suh I, Jee SH, Kim HC, Nam CM, Kim IS, Appel LJ. Low serum cholesterol and haemorrhagic stroke in men: Korea Medical Insurance Corporation Study. *LANCET* 2001; 357: 922-925

Tanihara S, Hayakawa T, Oki I, Nakamura Y, Sakata K, Okayama A, Fujita Y, Ueshima H; NIPPON DATA Research Group. Proteinuria is a prognostic marker for cardiovascular mortality: NIPPON DATA, 1980-1999. *J Epidemiol* 2005; 15: 146-153

Tsioufis C, Dimitriadis K, Antoniadis D, Stefanadis C, Kallikazaros I. Inter-relationships of microalbuminuria with the other surrogates of the atherosclerotic cardiovascular disease in hypertensive subjects. *Am J Hypertens* 2004; 17: 470-476

Yuyun MF, Khaw KT, Luben R, Welch A, Bingham S, Day NE, Wareham NJ. Microalbuminuria and stroke in a British population: the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) Population Study. *J Intern Med* 2004; 255: 247-256

Abstract in Korean

단백뇨 검출여부에 따른

혈압수준과 뇌졸중 위험의 연관성

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고혈압은 뇌졸중의 가장 중요한 위험 인자로 알려져 있다. 그 연관성에 관한 많은 연구가 있었으나, 단백뇨가 검출된 성인에서의 고혈압과 뇌졸중의 위험에 대해서는 연구가 부족하다. 추적 연구를 통해 단백뇨 검출여부에 따라 고혈압이 뇌출혈에 미치는 영향을 알아보았다.

본 연구는 Korea Medical Insurance Corporation (KMIC) 코호트 자료를 이용하였다. 연구대상은 1990년과 1992년 두 차례의 건강검진에 모두 참여한 35-59세의 남 102,672 명, 녀 60,443 명 이었다. 단백뇨 양성은 90년과 92년의 두 차례의 dipstick 검사상 한 번 이상의 결과가 1+ 이상으로 나온 것으로, 혈압 수준은 JNC-7 기준을 이용하여 비고혈압, 고혈압 제 1기, 제 2기로 구분하였다. 종속변수는 1993년부터 2004년의 추적관찰기간 동안 발생한 뇌출혈, 지주막하

출혈, 허혈성 뇌졸중으로 하였다. 뇌졸중 발생 위험 분석 위해 Cox의 비례위험 모델을 이용하여 검진 시 연령, 체질량 지수, 혈당농도, 콜레스테롤 농도, 흡연력, 음주량 등을 보정하고 상대위험도를 계산하였다.

남성에서 11년 동안 554 건의 뇌출혈, 152 건의 지주막하출혈, 1978 건의 허혈성 뇌졸중이 발생했다. 단백뇨의 상대위험도는 뇌출혈 2.60 (1.71-3.94), 지주막하출혈 0.44 (0.06-3.21), 허혈성 뇌졸중 1.16 (0.89-1.52) 이었다. 제2기 고혈압의 상대위험도는 뇌출혈 4.20 (3.15-5.61), 지주막하출혈 1.60 (0.98-2.45), 허혈성 뇌졸중 1.26 (1.10-1.46) 이었다. 단백뇨 미 검출 남성보다 단백뇨 검출 남성에서 혈압수준이 올라갈수록 뇌출혈 위험의 증가 폭이 현저 하였다. 이와 같은 결과는 다른 종류의 뇌졸중이나 여성에서는 발견할 수 없었다. 단백뇨 검출여부에 따라, 혈압 수준에 따른 뇌출혈 예측력 파악을 위한 ROC 분석에서 단백뇨가 검출된 남성에서 수축기 혈압 기준을 135mmHg로 할 때 뇌출혈 위험 예측력이 가장 큰 것으로 나타났다.

요약하면, 이 연구는, 단백뇨 검출 시, 남성에서 고혈압으로 인한 뇌출혈의 위험이 단백뇨 미 검출 시 보다 현저하게 증가하며, 뇌출혈 예방을 위한 적정 수준의 혈압조절과 아울러 단백뇨의 조기 발견과 조절이 큰 도움이 될 수 있음을 보여주었다.

핵심되는 말: 단백뇨, 고혈압, 뇌출혈