Longitudinal Blood Pressure Trajectory Patterns and Cardiovascular Mortality in Korean Adult Population

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Longitudinal Blood Pressure Trajectory Patterns and Cardiovascular Mortality in Korean Adult Population

A Master's Thesis

Submitted to the Department of Epidemiology and Health Promotion
and Graduate School of Public Health of Yonsei University

in partial fulfillment of the requirements

for the degree of Master of Public Health

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August 2020

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August 2020

ACKNOWLEDGEMENTS

I deeply appreciate all of you Prof. Sun Ha Jee, Keum Ji Jung, and Hyeon Chang Kim who helped me complete my Graduate School of Public Health, Yonsei University. It took very long time for me to finish all of the courses and this work. I am very grateful to Min-Kyung Han who advised and supported me to analyze various statistical methods. In addition, I would like to say to all of Professors in Graduate School of Public Health, Yonsei University for excellent classes. Most of all, I appreciate my wife, JiYeon, my son Ikjun and my daughter Yewon for waiting for completing my work without any complaints. I love all of you and I am very sorry for not being faithful to my family.

This research was supported by Clinical Trials Center of Incheon St. Mary's Hospital, The Catholic University of Korea.

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ABSTRACT

Longitudinal Blood Pressure Trajectory Patterns and Cardiovascular Mortality in Korean Adult Population

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Background : Longitudinal blood pressure (BP) trajectory patterns according to 2017 American College of Cardiology (ACC)/ American Heart Association (AHA) guideline and cardiovascular mortality is not fully elucidated in Korea.

Methods : The current population-based cohort study analyzing the NHIS-HEALS (National Health Insurance Service–National Health Screening Cohort) database, including 315 462 adults including cardiovascular diseases history, aged 42 to 82 years at baseline who had taken twice health examination including BP measurement from 2002 to 2005 was conducted. Eight BP categorical trajectory patterns (Stable Normal, Static Elevated, Static Hypertension (HTN), Unstable Elevated, Unstable HTN1, Unstable HTN2, Normalized, and Decreased) according to criteria change defined by 2017 ACC/AHA guideline for all-cause and cardiovascular mortality using Cox proportional hazard models were analyzed over a mean 10.1-year follow-up period according to age and sex.

Results : The Static HTN group showed increased hazards for all-cause mortality (P<0.001) and cardiovascular disease mortality (P<0.001) than those of the Stable Normal group in all adults. The Decreased group showed increased hazards for CVD-related death in adult men regardless of age, hemorrhagic stroke-related mortality in middle-aged women (<60 years) and ischemic stroke-related and hemorrhagic stroke-related mortality in elderly women (≥60 years) (all P values <0.001). The Unstable Elevated group showed a strong hazard of 7.21 (1.72-30.22) for hemorrhagic stroke-related mortality in middle-aged men (P<0.001).

Conclusion : The Decreased trajectory from the HTN Stage 1 or 2 to the Elevated criteria still showed increased CVD-related mortality in adult populations, especially hemorrhagic stroke-related mortality in women. The Normal to Elevated trajectory increased hemorrhagic stroke-related mortality in middle-aged men. Active BP control for these populations like blind spots may be necessary.

Keywords : blood pressure trajectory · age · sex · cardiovascular · stroke · mortality

I. INTRODUCTION

1. Background

Hypertension (HTN) is a major risk factor for death from all causes or cardiovascular disease (CVD).[1-3] Several studies have demonstrated the relationship between longitudinal blood pressure (BP) trajectories and cardiovascular mortality.[4-6] Recently, in South Korea, analyzing of National Health Insurance Service (NHIS) database, several studies about blood pressure and cardiovascular mortality have been published.[1,2] However, according to longitudinal BP trajectory patterns, a limited research about all-cause mortality and cardiovascular mortality has been studied in South Korea.[7] To reduce regression dilution bias, BP trajectory patterns with remeasurement over some particular time periods may increase the more accurate estimation of cardiovascular disease risk and mortality compared to those by single baseline BP measurement.[8,9]

2. Objectives

We aimed to elucidate whether the trajectory patterns of categorical change according to the 2017 American College of Cardiology/American Heart Association (ACC/AHA) HTN Clinical Practice Guidelines with risk of CVD affect cardiovascular mortality and all-cause mortality in Korean adult population through two times of health examinations at the different time periods.

II. METHODS

This study was approved by the Institutional Review Board at Incheon St. Mary's Hospital, the Catholic University of Korea (IRB number: OC19ZEDI0093).

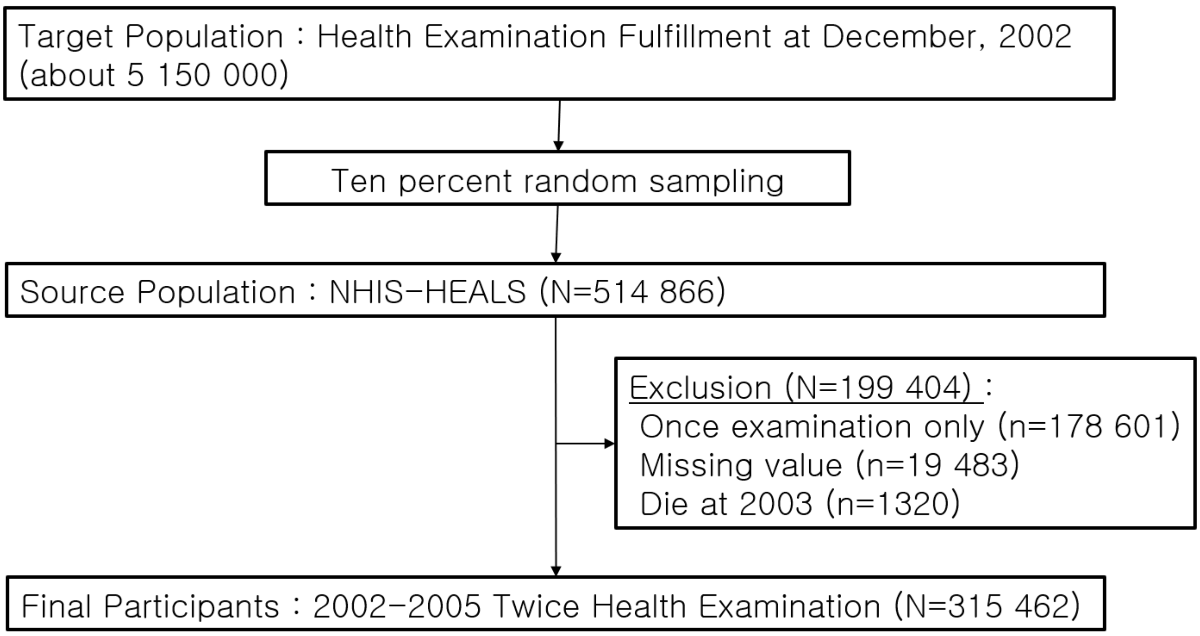
1. Study Populations

The Korean national health examination is conducted biannually using standardized self-reporting questionnaires including anthropometric parameters, BP measurement, lifestyle and laboratory tests. National Health Insurance Service (NHIS) provides mandatory health care system for all Korean people with 97% covering percentage. The National Health Insurance System-National Health Screening Cohort (NHIS-HEALS) database is comprised of baseline demographic records, health examination informatics, and follow-up death records including cause of deaths on those who had registered the NHIS and taken Korean national health examination from January 1, 2002, to December 31, 2015. Individuals who had been born in odd years underwent health check-up in odd years, and those who had been born in even years underwent health check-up in even years. Among about 5.15 million persons whose age was 40 to 79 years at the end of December, 2002, simple random sampling of 10% for target population had been conducted and final registered database consisted of 514,866 ones through deidentification. The epidemiological studies using NHIS database has been published and its validity is described elsewhere.[10]

2. Key Variables and Outcomes

During the health examination, all participants conducted BP measurements after taking a rest of at least 2 minutes in sitting position by digital or automatic monitors like as described elsewhere.[1] NHIS-HEALS data excluding those who died in 2003 (n=1320). During the period 1 (2002-2003) to Period 2 (2004-2005), those who completed two times health examination respectively were finally included in the final analysis (Figure).

Figure. Flow diagram of the study population



All patients were classified into 4 groups according to 2017 ACC/AHA criteria, including Normal (SBP < 120mmHg and DBP < 80mmHg), Elevated (120mmHg ≤ SBP < 130mmHg and DBP < 80mmHg), Stage 1 (130mmHg ≤ SBP <140mmHg or 80mmHg ≤ DBP<90mmHg), Stage 2 (SBP ≥140mmHg or DBP ≥ 90mmHg). Finally, BP trajectory patterns from first BP examination to second examination according to 2017 ACC/AHA hypertension criteria were reclassified into 1) Stable Normal (Normal to Normal), 2) Static Elevated (Elevated to Elevated) , 3) Static HTN (Stage 1 or 2 to Stage 1 or 2), 4) Unstable Elevated (Normal to Elevated), 5) Unstable HTN1 (Elevated to Stage 1 or 2), 6) Unstable HTN2 (Normal to Stage 1 or 2), 7) Normalized (Elevated or Stage 1 or 2 to Normal) 8) Decreased (Stage 1 or 2 to Elevated). The study index date was last health examination check-up date closed to January 1, 2006 for the second period. All baseline characteristics were recorded from the last health examination data.

The primary outcomes were all-cause or cardiovascular deaths. Follow-up duration was until December 31, 2015. Outcomes were identified from the data on the death certificate by the National Statistical Office. Death follow-up was conducted for about 100% of the study population. The cause of death was recorded according to the International Classification of Diseases, Tenth Revision (ICD-10). We used the underlying recorded causes of death in the current study. The ICD-10 codes recorded at the NHIS-HEALS database were reclassified into CVD (ICD-10 codes, I20-I25, I60-I69), coronary heart disease (CHD) (ICD-10 codes, I20-I25), ischemic stroke (ICD-10 codes, I63), and hemorrhagic stroke (ICD-10 codes, I60-I62).

3. Statistical Analysis

We tested the differences in eight categories using nonparametric Kruskal-Wallis Test and parametric Analysis of Variance test for continuous variables and Chi-square test for categorical variables. Multiple comparison was corrected using Tukey method. Analyses were performed adjusting for the following covariates: age at enrollment (continuous variable), sex (binary variable), and participation in physical activity (0, 1-2, 3-4, 5-6, 7 times/week), alcohol intake (0, <1, 1-2, 3-4, ≥5 times/week), body mass index (BMI) (four categories: <18.5, 18.5≤ and <23.0, 23.0≤ and <25.0, ≥25.0 kg/m^2), total cholesterol (<200, 200≤ and <240, ≥240mg/dL), fasting blood sugar (FBS) (mg/dL), past CVD history (no, heart disease, stroke), and smoking status (never, past, current smoker). Cox proportional hazard ratios were calculated for all-cause related, CVD related-, CHD related-, ischemic stroke related-, and hemorrhagic stroke-related deaths according to 2017 ACC/AHA HTN criteria trajectory. Proportional hazard assumption was test through graphic method and model using time-dependent explanatory variables. All proportional assumptions were not violated. Interactions between 2017 ACC/AHA HTN criteria trajectory and age or sex were tested and identified. Therefore, subgroup analyses were performed using cox proportional hazard models for all-cause related, CVD related-, CHD related-, ischemic stroke related-, and hemorrhagic stroke related death in adult men and women stratified by age group (60< or ≥60). P values of less than 0.05 were regarded as statistically significant. All analyses were conducted with the use of SAS software, version 9.4 (SAS Institute).

III. RESULTS

Among 514,866 persons in NHIS-HEALS source population, there were final 315 462 participants who completed health examination in both the period 1 (2002 to 2003) and the period 2 (2004 to 2005) excluding single examination, death at 2003, and missing values (Figure). Table 1 summarized the baseline characteristics of the study population. Mean age of the 315,462 participants was 54.5 (SD:9.2, median: 52, range 42-82) years. During the mean 10.1 follow-up year (SD 1.4), according to 2017 ACC/AHA HTN criteria trajectory, the orders of individual group size were Static HTN (157195, 49.8%), Normalized (44123, 14%), Stable Normal (41141, 13%), Unstable HTN2 (28946, 9.2%), Decreased (17209, 5.5%), Unstable HTN 1 (14420, 4.5%), Unstable elevated (8729, 2.8%), and Static Elevated (3899, 1.2%). Among the 2017 ACC/AHA HTN criteria trajectory, the age distributions in Static HTN, Unstable HTN, and Decreased group appeared higher than that in Stable Normal group (P<0.001). At the index date, mean SBP was highest in the Static HTN group and lowest in the Stable Normal group (P<0.001), and mean DBP was highest in the Static HTN group and lowest in the Stable Normal group (P<0.001). Proportions of women among the 2017 ACC/AHA hypertension criteria trajectories showed higher in the Stable Normal group than those in the other groups and the women proportion in the Static Hypertension group showed lower than those of the other groups (P<0.001 and P<0.001, respectively). Among the 2017 ACC/AHA hypertension criteria trajectories, CVD history, BMI, total cholesterol, FBS, smoking, physical activity, and alcohol drinking showed significant difference (P<0.001, respectively). A total of 21 657 deaths (crude death rate, 680 deaths per 100 000 person-years) occurred during 3 186 786 person-years (mean, 10.1 person-years) of follow-up, of which there were 3 106 CVD-related deaths (97.5 deaths per 100 000 person-years), 1 211 CHD-related deaths (38 deaths per 100 000 person-years), 594 ischemic stroke-related deaths (18.6 deaths per 100 000 person-years), and 637 hemorrhagic stroke-related deaths (20 deaths per 100 000 person-years).

Table 1. Baseline characteristics of the study population*

	Number of patients (%), 8 BP trajectories by 2017 ACC/AHA HTN guideline (N=315 462)§								
	Stable Normal (n=41 141)	Static Elevated (n=3 899)	Static HTN (n=157195)	Unstable Elevated (n=8729)	Unstable HTN 1 (n=14220)	Unstable HTN 2 (n=28946)	Normalized (n=44123)	Decreased (n=17209)	P value
Mean measurement interval, year (SD)	2.19 (0.46)	2.19 (0.47)	2.23 (0.51)	2.2 (0.47)	2.21 (0.48)	2.21 (0.49)	2.24 (0.5)	2.23 (0.49)	<.001
Age, median (IQR)	49 (45-56)	52 (46-62)	54 (48-62)	50 (46-58)	54 (47-62)	52 (46-60)	51 (46-59)	54 (47-62)	<.001
Sex									<.001
Men	16340 (39.7)	1974 (50.6)	101138 (64.3)	4054 (46.4)	8029 (56.5)	15456 (53.4)	23831 (54)	9982 (58)	
Women	24801 (60.3)	1925 (49.4)	56057 (35.7)	4675 (53.6)	6191 (43.5)	13490 (46.6)	20292 (46)	7227 (42)	
Past CVD history									<.001
None	40635 (98.7)	3810 (97.7)	153817 (97.8)	8595 (98.5)	13944 (98)	28486 (98.4)	43256 (98)	16767 (97.4)	
Heart disease	436 (1.1)	79 (2)	2454 (1.6)	108 (1.2)	207 (1.5)	353 (1.2)	714 (1.6)	336 (2)	
Stroke	70 (0.2)	10 (0.3)	924 (0.6)	26 (0.3)	69 (0.5)	107 (0.4)	153 (0.4)	106 (0.6)	
Blood pressure, mean (SD), mmHg									
SBPindex	106.1 (7.6)	122.6 (3)	136.5 (14.7)	122.2 (2.8)	131.5 (12)	127.7 (11.5)	108.7 (6.6)	122.4 (3)	<.001
DBPindex	66.4 (6)	71.1 (4.5)	85.7 (8.8)	71.1 (4.5)	82.4 (7.2)	82.1 (6.3)	68.3 (5.6)	71.4 (4.4)	<.001
BMI, mean (SD), kg/m^2									<.001
<18.5	1727 (4.2)	85 (2.2)	2301 (1.5)	233 (2.7)	284 (2)	704 (2.4)	1315 (3)	352 (2.1)	
18.5-22.9	21528 (52.3)	1489 (38.2)	45691 (29.1)	3825 (43.8)	4935 (34.7)	11317 (39.1)	18870 (42.8)	6057 (35.2)	
23.0-24.9	10536 (25.6)	1137 (29.1)	44541 (28.3)	2449 (28)	4021 (28.3)	8295 (28.7)	12200 (27.6)	4943 (28.7)	
≥25.0	7350 (17.9)	1188 (30.5)	64662 (41.1)	2222 (25.5)	4980 (35)	8630 (29.8)	11738 (26.6)	5857 (34)	
Total cholesterol, mean (SD), mg/dL									<.001
<200	25345 (61.6)	2180 (55.9)	79836 (50.8)	5021 (57.5)	7544 (53)	15892 (54.9)	25599 (58)	9453 (54.9)	
200.0-239.9	12126 (29.5)	1266 (32.5)	54581 (34.7)	2711 (31.1)	4720 (33.2)	9438 (32.6)	13792 (31.3)	5637 (32.8)	
≥240.0	3670 (8.9)	453 (11.6)	22778 (14.5)	997 (11.4)	1956 (13.8)	3616 (12.5)	4732 (10.7)	2119 (12.3)	
Fasting glucose, mean (SD), mg/dL	91.8 (20.5)	96.5 (23.7)	100.7 (30.7)	95.1 (26.5)	97.7 (28.1)	96.1 (27.3)	95.5 (26.7)	98.1 (27.2)	<.001
Smoking									<.001
Never	31427 (76.4)	2771 (71.1)	104632 (66.6)	6363 (72.9)	9871 (69.4)	20391 (70.5)	30761 (69.7)	11854 (68.9)	
Past	2787 (6.8)	367 (9.4)	16976 (10.8)	800 (9.2)	1434 (10.1)	2674 (9.2)	3937 (8.9)	1756 (10.2)	
Current	6927 (16.8)	761 (19.5)	35587 (22.6)	1566 (17.9)	2915 (20.5)	5881 (20.3)	9425 (21.4)	3599 (20.9)	
Physical activity, times/week									<.001
0	20974 (51)	1894 (48.6)	77079 (49)	4330 (49.6)	7231 (50.8)	15099 (52.2)	22296 (50.5)	8328 (48.4)	
1-2	11128 (27.1)	1034 (26.5)	42905 (27.3)	2337 (26.8)	3721 (26.2)	7714 (26.6)	11813 (26.8)	4694 (27.3)	
3-4	5136 (12.5)	529 (13.6)	19254 (12.3)	1099 (12.6)	1720 (12.1)	3371 (11.6)	5439 (12.3)	2181 (12.7)	
5-6	1297 (3.1)	137 (3.5)	4899 (3.1)	270 (3.1)	409 (2.9)	801 (2.8)	1420 (3.2)	576 (3.3)	
7	2606 (6.3)	305 (7.8)	13058 (8.3)	693 (7.9)	1139 (8)	1961 (6.8)	3155 (7.2)	1430 (8.3)	
Alcohol drinking,									<.001

times/week								
0	27731 (67.4)	2433 (62.4)	83254 (53)	5591 (64.1)	8260 (58.1)	17325 (59.9)	26655 (60.4)	10093 (5.6)
<1	6283 (15.3)	611 (15.7)	23528 (15)	1319 (15.1)	2084 (14.7)	4384 (15.1)	6856 (15.5)	2609 (15.2)
1-2	4975 (12.1)	536 (13.7)	30172 (19.2)	1200 (13.7)	2379 (16.7)	4595 (15.9)	6960 (15.8)	2812 (16.3)
3-4	1425 (3.4)	179 (4.6)	12766 (8.1)	386 (4.4)	921 (6.5)	1708 (5.9)	2321 (5.3)	1066 (6.2)
≥5	727 (1.8)	140 (3.6)	7475 (4.7)	233 (2.7)	576 (4)	934 (3.2)	1341 (3)	629 (3.7)

*BP, ACC/AHA, HTN, SD, IQR, CVD, SBPindex, and DBPindex mean hypertension, American College of Cardiology/American Heart Association, standard deviation, interquartile range, cardiovascular disease, systolic bloop pressure at index date, diastolic blood pressure at index date, respectively.

§ Stable Normal : Normal to Normal, Static Elevated : Elevated to Elevated, Static HTN : Stage I or II to Stage I or II, Unstable Elevated : Normal to Elevated, Unstable HTN 1 : Elevated to Stage I or II, Unstable HTN 2 : Normal to Stage I or II, Normalized : Elevated or Stage I or II to Normal.

Table 2 shows hazard ratios of all-cause and cardiovascular mortality according to 2017 ACC/AHA HTN criteria trajectory in middle-aged men (<60 years) and elderly men (≥60 years) after adjustment for age (continuous), BMI, FBS, total cholesterol, smoking, alcohol drinking, physical activity, past CVD history, and measurement interval of BPs.

1. Hazard Ratios for All-cause or Cardiovascular Death in Middle-aged Men (<60 years)

Adjusted HRs for all-cause mortality compared to the Stable Normal group were 1.35 (95% CI, 1.21-1.5) in the Static HTN group, 1.36 (95% CI, 1.15-1.16) in the Unstable HTN1 group, 1.14 (95% CI, 1.001-1.29) in the Normalized group, and 1.21 (95% CI, 1.04-1.42) in the Decreased group. For CVD-related death, adjusted HRs were 2.63 (95% CI, 1.74-3.97) in the Static HTN, 1.94 (95% CI, 1.08-3.47) in the Unstable HTN1 group, 1.78 (95% CI, 1.02-3.1) in the Decreased group. Regarding CHD-related death, the Static HTN group only showed a HR of 1.73 (1.05-2.83) but other groups did not. There was no statistically significant HRs for ischemic stroke-related death in any group. Adjusted HRs for hemorrhagic stroke-related death were 6.68 (95% CI, 2.1-21.23) in the Static HTN group and 7.21 (95% CI, 1.72-30.22) in the Unstable Elevated group (Table 2).

Table 2. Stratified analysis of cardiovascular mortality according to longitudinal categorical blood pressure trajectory patterns in middle-aged men (<60 years)*

Cause of Deaths	Number of patients (%), 8 BP trajectories by 2017 ACC/AHA HTN guideline (N=133483) §							
	Stable Normal (n=13447)	Static Elevated (n=1405)	Static HTN (n=72122)	Unstable Elevated (n=3147)	Unstable HTN 1 (n=5782)	Unstable HTN 2 (n=12056)	Normalized (n=18423)	Decreased (n=7101)
All cause-related								
Deaths	399	38	2890	100	224	397	614	255
Person-years	137746	14402	735986	32208	59033	123876	187802	72559
Mortality (deaths/100000 person-years)	289.7	263.9	392.6	310.5	379.4	320.5	326.9	351.4
Adjusted HR (95% CI) §§	1 (Reference)	0.95 (0.68-1.32	1.35 (1.21-1.5)	1.1 (0.88-1.37)	1.36 (1.15-1.6)	1.14 (0.99-1.31)	1.14 (1.001-1.29)	1.21 (1.04-1.42)
CVD-related								
Deaths	25	4	373	10	21	33	46	25
Person-years	137746	14402	735986	32208	59033	123876	187802	72559
Mortality (deaths/100000 person-years)	18.1	27.8	50.7	31	35.6	26.6	24.5	34.5
Adjusted HR (95% CI) §§	1 (Reference)	1.5 (0.52-4.32)	2.63 (1.74-3.97)	1.73 (0.83-3.61)	1.94 (1.08-3.47)	1.46 (0.87-2.46)	1.32 (0.81-2.15)	1.78 (1.02-3.1)
CHD-related								
Deaths	18	3	177	5	12	22	28	18
Person-years	137746	14402	735986	32208	59033	123876	187802	72559
Mortality (deaths/100000 person-years)	13.1	20.8	24	15.5	20.3	17.8	14.9	24.8
Adjusted HR (95% CI) §§	1 (Reference)	1.5 (0.44-5.09)	1.73 (1.05-2.83)	1.21 (0.45-	1.21 (0.45-	1.53 (0.73-3.19)	1.34 (0.72-2.5)	1.78 (0.92-3.42)

				3.26)	3.26)			
Ischemic stroke-related								
Deaths	3	0	31	0	2	1	10	1
Person-years	137746	14402	735986	32208	59033	123876	187802	72559
Mortality (deaths/100000 person-years)	2.2	NA	4.2	NA	3.4	0.8	5.3	1.4
Adjusted HR (95% CI) §§	1 (Reference)	NA	1.59 (0.47-5.31)	NA	1.44 (0.24-8.71)	0.35 (0.04-3.36)	2.21 (0.6-8.06)	0.52 (0.05-4.99)
Hemorrhagic stroke-related								
Deaths	3	1	108	5	5	7	4	5
Person-years	137746	14402	735986	32208	59033	123876	187802	72559
Mortality (deaths/100000 person-years)	2.2	6.9	14.7	15.5	8.5	5.7	2.1	6.9
Adjusted HR (95% CI) §§	1 (Reference)	3.38 (0.35-32.52)	6.68 (2.1-21.23)	7.21 (1.72-30.22)	4.01 (0.95-16.85)	2.65 (0.68-10.25)	0.99 (0.22-4.44)	3.16 (0.75-13.28)

*BP, ACC/AHA, HTN, HR, and CI mean blood pressure, American College of Cardiology/American Heart Association, hypertension, hazard ratio, and confidence interval, respectively.

§Stable Normal : Normal to Normal, Static Elevated : Elevated to Elevated, Static HTN : Stage I or II to Stage I or II, Unstable Elevated : Normal to Elevated, Unstable HTN 1 : Elevated to Stage I or II, Unstable HTN 2 : Normal to Stage I or II, Normalized : Elevated or Stage I or II to Normal, CVD-related : I20-I25, I60-I69, CHD-related : I20-I25, Ischemic stroke-related : I63, Hemorrhagic stroke-related : I60-I62

§§ Hazard ratio calculated after adjustment of age (continuous), BMI, fasting glucose, total cholesterol, smoking, alcohol drinking, physical activity, past cardiovascular history, and measurement interval of blood pressure.

2. Hazard Ratios for All-cause or Cardiovascular Death in Elderly Men (≥60 years)

Adjusted HRs for all cause-related death compared to the Stable Normal group were 1.2 (95% CI, 1.1-1.31) in the Static HTN group and 1.12 (95% CI, 1.02-1.24) in the Normalized group. Regarding CVD-related deaths, adjusted HRs were 1.86 (95% CI, 1.43-2.42) in the Static HTN group and 1.56 (95% CI, 1.12-2.16) in the Decreased group. However, there were no significant HRs for ischemic stroke-related deaths in any 2017 ACC/AHA HTN trajectory groups. For hemorrhagic stroke-related death, adjusted HRs were 8.5 (95%CI, 2.03-35.63) in the Static Elevated group and 6.3 (95% CI, 2-19.81) in the Static HTN group (Table 2).

Table 3 shows HRs for all-cause and cardiovascular mortality according to 2017 ACC/AHA HTN trajectories in adult middle-aged women and adult elderly women after adjustment for age (continuous), BMI, FBS, total cholesterol, smoking, alcohol drinking, physical activity, past CVD history, and measurement interval of BPs.

Table 3. Stratified analysis of cardiovascular mortality according to longitudinal categorical blood pressure trajectory patterns in elderly men (≥60 years)*

Cause of Deaths	Number of patients (%),8 BP trajectories by 2017 ACC/AHA HTN guideline (N=47321)							
	Stable Normal (n=2893)	Static Elevated (n=569)	Static HTN (n=29016)	Unstable Elevated (n=907)	Unstable HTN 1 (n=2247)	Unstable HTN 2 (n=3400)	Normalized (n=5408)	Decreased (n=2881)
All cause-related								
Deaths	601	115	6482	200	477	759	1231	609
Person-years	27313	5435	274312	8614	21324	32270	50652	27196
Mortality (deaths/100000 person-years)	2200.4	2115.9	2363	2321.8	2236.9	2352	2430.3	2239.3
Adjusted HR (95% CI) §§	1 (Reference)	0.97 (0.79-1.18)	1.2 (1.1-1.31)	1.01 (0.86-1.19)	1.02 (0.9-1.15)	1.09 (0.98-1.21)	1.12 (1.02-1.24)	1.07 (0.95-1.2)
CVD-related								
Deaths	60	16	1022	22	59	92	129	92
Person-years	27313	5435	274312	8614	21324	32270	50652	27196
Mortality (deaths/100000 person-years)	219.7	294.4	372.6	255.4	276.7	285.1	254.7	338.3
Adjusted HR (95% CI) §§	1 (Reference)	1.36 (0.78-2.35)	1.86 (1.43-2.42)	1.15 (0.7-1.87)	1.23 (0.86-1.76)	1.32 (0.95-1.82)	1.18 (0.87-1.6)	1.56 (1.12-2.16)
CHD-related								
Deaths	32	8	368	14	29	42	65	28
Person-years	27313	5435	274312	8614	21324	32270	50652	27196

Mortality (deaths/100000 person-years)	117.2	147.2	134.2	162.5	136	130.2	128.3	103
Adjusted HR (95% CI) §§	1 (Reference)	1.3 (0.6-2.82)	1.32 (0.92-1.91)	1.43 (0.76-2.69)	1.21 (0.73-2.01)	1.17 (0.73-1.85)	1.13 (0.74-1.72)	0.93 (0.56-1.55)
Ischemic stroke-related								
Deaths	15	1	228	5	12	20	22	24
Person-years	27313	5435	274312	8614	21324	32270	50652	27196
Mortality (deaths/100000 person-years)	54.9	18.4	83.1	58	56.3	62	43.4	88.2
Adjusted HR (95% CI) §§	1 (Reference)	0.33 (0.04-2.5)	1.57 (0.92-2.66)	0.99 (0.36-2.73)	0.93 (0.43-1.98)	1.1 (0.56-2.15)	0.78 (0.41-1.51)	1.53 (0.8-2.93)
Hemorrhagic stroke-related								
Deaths	3	5	172	3	3	9	13	7
Person-years	27313	5435	274312	8614	21324	32270	50652	27196
Mortality (deaths/100000 person-years)	11	92	62.7	34.8	14.1	27.9	25.7	25.7
Adjusted HR (95% CI) §§	1 (Reference)	8.5 (2.03-35.63)	6.3 (2-19.81)	3.12 (0.63-15.47)	1.27 (0.26-6.29)	2.61 (0.71-9.65)	2.37 (0.67-8.31)	2.39 (0.62-9.28)

*BP, ACC/AHA, HTN, HR, and CI mean blood pressure, American College of Cardiology/American Heart Association, hypertension, hazard ratio, and confidence interval, respectively.

§Stable Normal : Normal to Normal, Static Elevated : Elevated to Elevated, Static HTN : Stage I or II to Stage I or II, Unstable Elevated : Normal to Elevated, Unstable HTN 1 : Elevated to Stage I or II, Unstable HTN 2 : Normal to Stage I or II, Normalized : Elevated or Stage I or II to Normal, CVD-related : I20-I25, I60-I69, CHD-related : I20-I25, Ischemic stroke-related : I63, Hemorrhagic stroke-related : I60-I62

§§ Hazard ratio calculated after adjustment of age (continuous), BMI, fasting glucose, total cholesterol, smoking, alcohol drinking, physical activity, past cardiovascular history, and measurement interval of blood pressure.

3. Hazard Ratios for All-cause or Cardiovascular Death in Middle-aged Women (<60 years)

Adjusted HRs for all cause-related deaths were 1.27 (95% CI, 1.09-1.49) in the Static HTN group, 1.42 (95% CI, 1.1-1.83) in the Decreased group compared to the Stable Normal group. For the CVD-related deaths, adjusted HRs in the Static HTN group was 1.89 (95% CI, 1.13-3.16) but the other groups showed no statistically significant HRs. For the CHD-related and ischemic stroke-related deaths, there was no statistically significant variables. For the hemorrhagic stroke-related death, adjusted HRs were 5.29 (95% CI, 2.05-13.64) in the Static HTN group, 4.37 (95% CI, 1.25-15.2) in the Decreased group (Table 4).

Table 4. Stratified analysis of cardiovascular mortality according to longitudinal categorical blood pressure trajectory patterns in middle-aged women (<60 years)*

Cause of Deaths	Number of patients (%),8 BP trajectories by 2017 ACC/AHA HTN guideline (N=89121)							
	Stable Normal (n=20954)	Static Elevated (n=1270)	Static HTN (n=30908)	Unstable Elevated (n=3536)	Unstable HTN 1 (n=3704)	Unstable HTN 2 (n=9560)	Normalized (n=14719)	Decreased (n=4470)
All cause-related								
Deaths	236	17	530	40	55	139	195	81
Person-years	217262	13155	319160	36591	38332	99205	152007	46019
Mortality (deaths/100000 person-years)	108.6	129.2	166.1	109.3	143.5	140.1	128.3	176
Adjusted HR (95% CI) §§	1 (Reference)	1.08 (0.66-1.76)	1.27 (1.09-1.49)	0.95 (0.68-1.33)	1.17 (0.87-1.57)	1.2 (0.97-1.49)	1.11 (0.92-1.34)	1.42 (1.1-1.83)
CVD-related								
Deaths	20	1	77	2	6	9	15	9
Person-years	217262	13155	319160	36591	38332	99205	152007	46019
Morality (deaths/100000 person-years)	9.2	7.6	24.1	5.5	15.7	9.1	9.9	19.6
Adjusted HR (95% CI) §§	1 (Reference)	0.69 (0.09-5.16)	1.89 (1.13-3.16)	0.53 (0.12-2.28)	1.34 (0.54-3.36)	0.86 (0.39-1.89)	0.95 (0.48-1.86)	1.67 (0.75-3.68)
CHD-related								
Deaths	8	0	17	0	4	2	3	3
Person-years	217262	13155	319160	36591	38332	99205	152007	46019
Morality	3.7	NA	5.3	NA	10.4	2	2	6.5

(deaths/100000 person-years)								
Adjusted HR (95% CI) §§	1 (Reference)	NA	0.79 (0.33-1.93)	NA	1.85 (0.55-6.28)	0.41 (0.09-1.94)	0.42 (0.11-1.59)	1.15 (0.3-4.41)
Ischemic stroke-related								
Deaths	4	0	12	0	0	1	1	0
Person-years	217262	13155	319160	36591	38332	99205	152007	46019
Morality (deaths/100000 person-years)	1.8	NA	3.8	NA	NA	1	0.7	NA
Adjusted HR (95% CI) §§	1 (Reference)	NA	1.01 (0.3-3.36)	NA	NA	0.39 (0.04-3.5)	0.27 (0.03-2.44)	NA
Hemorrhagic stroke-related								
Deaths	5	1	42	2	2	4	7	5
Person-years	217262	13155	319160	36591	38332	99205	152007	46019
Mortality (deaths/100000 person-years)	2.3	7.6	13.2	5.5	5.2	4	4.6	10.9
Adjusted HR (95% CI) §§	1 (Reference)	3.22 (0.38-27.64)	5.29 (2.05-13.64)	2.35 (0.46-12.12)	2.15 (0.41-11.14)	1.73 (0.46-6.48)	1.93 (0.61-6.09)	4.37 (1.25-15.2)

*BP, ACC/AHA, HTN, HR, and CI mean blood pressure, American College of Cardiology/American Heart Association, hypertension, hazard ratio, and confidence interval, respectively.

§Stable Normal : Normal to Normal, Static Elevated : Elevated to Elevated, Static HTN : Stage I or II to Stage I or II, Unstable Elevated : Normal to Elevated, Unstable HTN 1 : Elevated to Stage I or II, Unstable HTN 2 : Normal to Stage I or II, Normalized : Elevated or Stage I or II to Normal, CVD-related : I20-I25, I60-I69, CHD-related : I20-I25, Ischemic stroke-related : I63, Hemorrhagic stroke-related : I60-I62

§§ Hazard ratio calculated after adjustment of age (continuous), BMI, fasting glucose, total cholesterol, smoking, alcohol drinking, physical activity, past cardiovascular history, and measurement interval of blood pressure.

4. Hazard Ratios for All-cause or Cardiovascular Death in Elderly Women (≥60 years)

The adjusted significant HR for all-cause death was 1.18 (95% CI, 1.05-1.32) in the Static HTN group but the other groups showed no statistically significant HRs compared to the Stable Normal group (Table 3). For CVD-related deaths, adjusted HRs was 2 (95% CI, 1.09-3.69) in the Static Elevated group, and 1.88 (95% CI, 1.35-2.6) in the Static HTN group, 1.98 (95% CI, 1.32-2.96) in the Unstable HTN1 group, and 1.57 (95% CI, 1.03-2.38) in the Decreased group (Table 5).

Table 5. Stratified analysis of cardiovascular mortality according to longitudinal categorical blood pressure trajectory patterns in elderly women (≥60 years)*

Cause of Deaths	Number of patients (%),8 BP trajectories by 2017 ACC/AHA HTN guideline (N=45537)							
	Stable Normal (n=3847)	Static Elevated (n=655)	Static HTN (n=25149)	Unstable Elevated (n=1139)	Unstable HTN 1 (n=2487)	Unstable HTN 2 (n=3930)	Normalized (n=5573)	Decreased (n=2757)
All cause-related								
Deaths	325	65	2995	87	252	414	563	272
Person-years	38719	6550	250366	11556	24981	39251	55487	27417
Mortality (deaths/100000 person-years)	839.4	992.4	1196.2	752.9	1008.767	1054.8	1014.7	992.1
Adjusted HR (95% CI) §§	1 (Reference)	1.14 (0.88-1.49)	1.18 (1.05-1.32)	0.86 (0.68-1.09)	1.04 (0.88-1.23)	1.11 (0.96-1.28)	1.08 (0.94-1.24)	1.04 (0.88-1.22)
CVD-related								
Deaths	39	14	613	13	61	64	82	52
Person-years	38719	6550	250366	11556	24981	39251	55487	27417
Mortality (deaths/100000 person-years)	100.7	213.7	244.8	112.5	244.2	163.1	147.8	189.7
Adjusted HR (95% CI) §§	1 (Reference)	2 (1.09-3.69)	1.88 (1.35-2.6)	1.06 (0.56-1.98)	1.98 (1.32-2.96)	1.36 (0.91-2.03)	1.26 (0.86-1.85)	1.57 (1.03-2.38)
CHD-related								
Deaths	19	4	200	4	20	16	24	18
Person-years	38719	6550	250366	11556	24981	39251	55487	27417
Mortality	49.1	61.1	79.9	34.6	80.1	40.8	43.3	65.7

(deaths/100000 person-years)								
Adjusted HR (95% CI) §§	1 (Reference)	1.16 (0.39-3.41)	1.25 (0.78-2.02)	0.69 (0.23-2.02)	1.32 (0.7-2.48)	0.7 (0.36-1.37)	0.75 (0.41-1.36)	1.11 (0.58-2.12)
Ischemic stroke-related								
Deaths	6	3	121	3	11	18	24	15
Person-years	38719	6550	250366	11556	24981	39251	55487	27417
Mortality (deaths/100000 person-years)	15.5	45.8	48.3	26	44	45.9	43.3	54.7
Adjusted HR (95% CI) §§	1 (Reference)	2.68 (0.67-10.72)	2.21 (0.97-2.06)	1.5 (0.37-6.01)	2.2 (0.81-5.97)	2.38 (0.94-6.02)	2.26 (0.92-5.55)	2.7 (1.04-6.99)
Hemorrhagic stroke-related								
Deaths	7	4	137	3	16	19	16	14
Person-years	38719	6550	250366	11556	24981	39251	55487	27417
Mortality (deaths/100000 person-years)	18.1	61.1	54.7	26	64.0	48.4	28.8	51.1
Adjusted HR (95% CI) §§	1 (Reference)	3.38 (0.99-11.55)	2.7 (1.26-5.8)	1.45 (0.38-5.63)	3.23 (1.33-7.88)	2.43 (1.02-5.79)	1.52 (0.62-3.69)	2.65 (1.07-6.6)

*BP, ACC/AHA, HTN, HR, and CI mean blood pressure, American College of Cardiology/American Heart Association, hypertension, hazard ratio, and confidence interval, respectively.

§Stable Normal : Normal to Normal, Static Elevated : Elevated to Elevated, Static HTN : Stage I or II to Stage I or II, Unstable Elevated : Normal to Elevated, Unstable HTN 1 : Elevated to Stage I or II, Unstable HTN 2 : Normal to Stage I or II, Normalized : Elevated or Stage I or II to Normal, CVD-related : I20-I25, I60-I69, CHD-related : I20-I25, Ischemic stroke-related : I63, Hemorrhagic stroke-related : I60-I62

§§ Hazard ratio calculated after adjustment of age (continuous), BMI, fasting glucose, total cholesterol, smoking, alcohol drinking, physical activity, past cardiovascular history, and measurement interval of blood pressure.

IV. DISCUSSIONS

The current study demonstrated that the longitudinal trajectories according to 2017 ACC/AHA HTN criteria had different risks for all-cause and cardiovascular mortality. When compared to the Stable Normal BP subjects, especially, among middle-aged populations, the Static HTN group showed increased hazards for all-cause related and CVD-related death compared to that of the Stable Normal group in all adult groups. The Decreased group showed increased hazards for CVD-related death in adult men regardless of age, for hemorrhagic stroke-related death in middle-aged women and for both ischemic stroke-related and hemorrhagic stroke-related death in elderly women. The Unstable Elevated group showed a strong hazard for hemorrhagic stroke-related death in middle-aged men.

Several studies previously reported cardiovascular mortality according to longitudinal BP trajectory.[4,5,7,11] The 2017 ACC/AHA HTN guideline from the previous 2003 Joint National Committee (JNC) 7 guideline was the major definition change of hypertension cutoff value from greater or equal to 140/90mmHg to 130/80mmHg.[12,13] Fan et al. demonstrated that using JNC 7 criteria, relative to stable BP of normotension, BP increase from normotension to prehypertension or from prehypertension to hypertension had an increased risk of all-cause (HR, 1.36;95% CI, 1.23-1.51), CVD-related (HR, 1.55; 95% CI, 1.24-1.93), and stroke-related (HR, 2.61; 95% CI, 2.11-3.24) mortality in a Chinese cohort.[4] In the current study, we divided longitudinal BP categorical change into 8 trajectories according to 2017

ACC/AHA HTN criteria and can be subsequently reclassified into three patterns like as BP unchanged, BP rise, and BP drop patterns.

1. BP Unchanged Pattern (Static Elevated, Static HTN)

When longitudinal trajectory of the Static Elevated (Elevated to Elevated) in elderly persons (≥60 years), men had a significant increased risk for hemorrhagic stroke-related death and women did a significantly increased risk for CVD-related death (Table 3 and 5). Fan et al. showed according to JNC7 criteria in the longitudinal BP change study that stable prehypertension had a HR of 1.75 (95% CI, 1.29-2.39) for CVD-related mortality but had a HR of 1.34 (95% CI, 0.92-1.96).[4] However, Xie et al. reported that elevated BP (120≤SBP<130 and DBP<80) had had HR of 1.103 (95% CI, 0.804-1.515) for CVD mortality.[14] Qi et al. also demonstrated in another Chinese population study according to 2017 ACC/AHA guideline that HRs of CVD incidence, CHD incidence, stroke incidence, and CVD mortality had 1.51 (95% CI, 1.2-1.89), 1.56 (95% CI, 1.09-2.25), 1.48 (95% CI, 1.12-1.97), and 1.32 (95% CI, 0.75-2.31), respectively.[15] Therefore, whether those aged more than 60 years who have persistent elevated BP over some particular periods should be included in a targeting population to control BP aggressively, it needs to be further studied.

On the other hand, longitudinal trajectory of the Static HTN (persistent stage 1 or 2) in the current study showed significantly increased risks for CVD-related death, hemorrhagic stroke-related death, and all-cause death in all adults (Table 2, 3, 4, and 5). According to the 2017 ACC/AHA guideline, two Chinese studies revealed that stage 1 and stage 2 HTN had increased hazards of all cause-mortality, CVD mortality, stroke incidence, and myocardial infarction (MI) or CHD incidence.[14,15]

2. BP Rise Pattern (Unstable Elevated, Unstable HTN1, Unstable HTN2)

When longitudinal BP rise from the Normal BP to the Elevated BP, middle-aged men only had a significantly increased risk for hemorrhagic stroke-related death in the current study (Table 2). In the longitudinal trajectory of the Unstable HTN1 (Elevated to HTN Stage 1 or 2), middle-aged men and elderly women had significantly increased risk for CVD-related death, and elderly women also had increased risk for hemorrhagic stroke-related death (Table 2 and Table 5). In the longitudinal trajectory of the Unstable HTN2 (Normal to Stage 1 or 2), elderly women only had a significant increased risk for hemorrhagic stroke-related death (Table 5). Fan et al. revealed according to JNC7 criteria that those whose BP had changed from normotension to prehypertension had HRs of 1.1 (95% CI, 0.98-1.22), 1.32 (95% CI, 1.04-1.68), and 1.14 (95% CI, 0.88-1.48) for all-cause mortality, CVD mortality, and stroke mortality, respectively.[4] This longitudinal Chinese study also showed that HRs of prehypertension to hypertension and normotension to hypertension had 1.36 (95% CI, 1.23-1.51) and 1.22 (95% CI, 1.12-1.34) for all-cause mortality, 1.55 (95% CI, 1.24-1.93) and 1.32 (95% CI, 1.04-1.68) for CVD mortality, 2.61 (95% CI, 2.11-3.24) and 2.29 (95% CI, 1.88-2.8) for stroke mortality, respectively.[4]

3. BP Drop Pattern (Normalized, Decreased)

When longitudinal BP drops from the Elevated/Stage 1/Stage 2 to the Normal BP, there was no risk for CVD-related death, CHD-related, ischemic stroke-related, or hemorrhagic stroke-related death (Table 2, 3, 4, 5). With the longitudinal BP drop from the Stage 1/Stage 2 to Elevated BP, all adults had still increased risks of CVD-related death, and increased risk of hemorrhagic stroke-related death in case of middle-aged women, but in case of elderly women, there were increased risks for ischemic stroke-related death and hemorrhagic stroke-related death, respectively (Table 2, 3, 4, 5). In a Chinese longitudinal BP study, according to JNC 7 criteria, prehypertension to normotension had still increased HRs without statistical significance of 1.15 (95% CI, 0.96-1.38) for all-cause mortality, 1.38 (95% CI, 0.96-2.0) for CVD mortality, 1.04 (96% CI, 0.66-1.63) for stroke mortality, respectively.[4] However, in this Chinese study did not investigated mortalities for those from hypertension to normotension or hypertension to prehypertension criteria according to JNC 7 criteria.[4] However, our results implicate that enough BP decrease from HTN to normotension may get rid of CVD mortality risks but insufficient BP decrease may have still hazards for CVD mortality.

This study has several limitations. Firstly, outcome mortalities are relatively low in the current study. In an individual data meta-analysis for one million adults in 61 prospective studies, CVD-related mortality, CHD-related mortality, and stroke-related mortality were much higher than those in our study.[16] Healthy populations might be predominantly included because those who had taken regular health examinations could have had more interests in health. Therefore, we should take a caution to interpret our results. Secondly, sample size was relatively small because death events from CHD and ischemic stroke did not occur in adult middle-aged men and women (Table 2 and 3). Thirdly, we did not include antihypertensive medication history over the two times measurement of BPs. Son et al. showed that antihypertensive medications during 5-year follow-up period decreased HRs for cardiovascular events.[1] The effect of antihypertensive medication on the 2017 ACC/AHA HTN trajectories may be necessary to be investigated further in the future.

V. CONCLUSIONS

Among middle-aged adult populations, the Static HTN group showed increased mortality from all causes and cardiovascular disease compared to those of the Stable Normal group in all adult groups. The Decreased BP group from the HTN Stage 1 or 2 but not reaching normal value showed increased CVD-related mortality in adult men regardless of age, hemorrhagic stroke-related mortality in middle-aged women, and ischemic stroke-related and hemorrhagic stroke-related mortality in elderly women. The Normal to Elevated BP group was associated with hemorrhagic stroke-related mortality in middle-aged men. This study implicates that age-specific active blood pressure management may be necessary for prevention of cardiovascular mortality.

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ABSTRACT (IN KOREAN)

한국인 성인에서 종적 혈압 궤적 양상과 심뇌혈관계 사망률

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서론 : 2017년 미국 심장학회/미국심장협회의 가이드라인에 따른 종적 혈압 궤적 양상과 심혈관사망에 대해서 한국에서는 충분히 밝혀지지 않은 상태이다.

방법 : 본 인구단위 코호트 연구는 2002년부터 2005년간 두 차례의 건강검진을 받은 42세에서 82세까지의 심혈관질환 병력을 포함하는 성인 315,462명을 대상으로 NHIS-HEALS데이터를 분석하여 수행되었다. 2017년 미국심장학회/미국심장협회의 가이드라인에 따른 혈압의 범주변화에 따라 8개의 혈압 범주 궤적 양상 (안정 정상, 정적 상승, 정적 고혈압, 불안정 상승, 불안정 고혈압1, 불안정 고혈압2, 정상화, 감소)을 나이와 성별에 따른 평균 10.1년의 추적기간동안 콕스비례위험모형을 이용하여 모든 원인에 의한 사망률과 심혈관사망률에 대해 분석하였다.

결과 : 정적고혈압그룹은 안정 정상 그룹에 비해 모든 사망률 (P<0.001) 및

심혈관질환 사망률 (P<0.001)에 대한 증가된 위험을 보였다. 감소그룹은 나이와 상관없이 성인남자에서는 심혈관질환 사망에 대한 증가된 위험을 보였고 중년 여성 (60세미만)에서는 출혈성 뇌줄중에 대해, 고령 여성 (60세 이상)에서는 허혈성 뇌졸중과 출혈성 뇌졸중에 유의한 증가된 위험을 보였다 (모든 P<0.001). 불안정 상승그룹은 중년 남성에서 출혈성 사망에 대한 7.21배 (95% 신뢰구간 1.72에서 30.22)의 강한 위험을 보였다.

결론 : 2017년 미국심장학회/미국심장협회 고혈압 1 또는 2단계에서 상승 범주로 혈압의 감소 궤적군은 성인인구에서 뇌졸중관련 증가된 사망률을 보였고 특히 여성에서는 출혈성 뇌졸중의 위험이 증가되었다. 혈압정상군에서 혈압상승군으로 혈압궤적의 변화는 중년 남성에서 출혈성 뇌졸중의 사망률을 증가시켰다. 이러한 사각지대에 있는 인구에 대한 적극적인 혈압조절이 필요할 수 있다.

핵심단어 : 혈압궤적, 나이, 성별, 심혈관질환, 뇌졸중, 사망률