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Doctor of Medicine

**Stage 1 Hypertension Defined by ACC/AHA 2017 Guideline
is Related to Asymptomatic Coronary Atherosclerosis**

**The Graduate School
Of the University of Ulsan
Department of Medicine
Yong-Hoon Yoon**

**Stage 1 Hypertension Defined by ACC/AHA 2017 Guideline
is Related to Asymptomatic Coronary Atherosclerosis**

Supervisor: Seung-Whan Lee

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By

Yong-Hoon Yoon

Department of Medicine

Ulsan, Korea

February 2020

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is Related to Asymptomatic Coronary Atherosclerosis**

This certifies that the dissertation
of Yong-Hoon Yoon is approved.

Young-Hak Kim

Committee Chair Dr.

Seung-Whan Lee

Committee Member Dr.

Jae-Hwan Lee

Committee Member Dr.

Jong-Young Lee

Committee Member Dr.

Gyung-Min Park

Committee Member Dr.

Department of Medicine

Ulsan, Korea

February 2020

ABSTRACT

Background

The evidence of relationship between stage 1 hypertension defined by ACC/AHA 2017 guideline and subclinical coronary atherosclerosis on coronary computed tomography angiography (CCTA) is lacking.

Method

A total of 4666 individuals with CCTA result as a health checkup were enrolled in this study. Hypertension category was defined according to ACC/AHA 2017 guideline. The presence of coronary plaque and its characteristics, coronary artery calcium (CAC) score, and significant stenosis defined as luminal narrowing > 50% were assessed.

Result

The mean age was 52.6 ± 7.3 years and 3311 (71.0%) were men. The patients were classified into 4 groups; normal, 2395 (51.3%); elevated, 467 (10.0%); stage 1 hypertension, 1139 (24.4%); and stage 2 hypertension, 665 (14.2%). The incidence of CT findings including high CAC score, all types of coronary plaque, significant stenosis were tended to be higher as increasing BP groups. When compared to normal group after multivariate adjustment, stage 1 and 2 hypertensions were significantly associated with the presence of atherosclerotic plaque (adjusted OR, 1.38 [1.17 – 1.63]; $P = 0.0001$ and adjusted OR, 1.66 [1.36 – 2.03]; $P < 0.0001$) especially in non-calcified and mixed plaque. Significant stenosis was found to be significantly higher only in stage 2 hypertension, but not in stage 1 hypertension. Elevated BP group was not associated with any positive CCTA findings. Systolic BP and diastolic BP in continuous level showed linear relationship with the risk of coronary plaque.

Conclusion

The stage 1 hypertension defined by ACC/AHA 2019 guideline (systolic BP 130 – 139 mmHg, diastolic BP 80 – 89 mmHg) was independently associated with subclinical coronary atherosclerosis.

Key words: hypertension, coronary atherosclerosis, coronary computed tomography angiography

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ABBREVIATIONS

ACC = American College of Cardiology

AHA = American Heart Association

BP = blood pressure

CAC = coronary artery calcium

CAD = coronary artery disease

CCTA = coronary computed tomography angiography

ESC = European Society of Cardiology

ESH = European Society of Hypertension

HDL = high density lipoprotein

hsCRP = high sensitivity C-reactive protein

LDL = low density lipoprotein

SIS = segment involvement scores

SSS = segment stenosis scores

INTRODUCTION

Hypertension is one of the major risk factors established around the world for various cardiovascular diseases and mortality.¹⁾ There is a lot of evidence to support this, and many studies have tried to control blood pressure at specific level and then reduce subsequent cardiovascular events.²⁻⁵⁾ Accordingly, the threshold and target of hypertension by different working groups have shifted over time.⁶⁾ Recently, the ACC/AHA 2017 guideline changed the lower limit of high blood pressure from 140/90mm Hg to 130/80mm Hg.⁷⁾ This change possibly identifies new hypertension patients up to 14% in US population.⁸⁾ On the contrary, the ESC/ESH guideline did not change the threshold of hypertension in 2018.⁹⁾ Thus, there is still ongoing debate over which population should be managed by BP lowering treatment and how low blood pressure (BP) should be targeted. Thus, understanding patients defined by the ACC/AHA 2017 guideline as stage 1 hypertension have become important in clinical practice in terms of risk prediction, subclinical disease progression, and proper treatment indication.

Coronary computed tomography angiography (CCTA) is a non-invasive diagnostic imaging modality for the patients suspected coronary artery disease (CAD) and has been validated from many publications.¹⁰⁾ It has advantage of non-invasiveness, which in turn can be used for patients at low cardiovascular risk. Therefore, this study assessed subclinical coronary atherosclerosis according to BP status in asymptomatic population who underwent CCTA as a modality in health checkup.

METHODS

Study Design and Population

A total of 9269 individuals over 20 years underwent self-referral CCTA evaluation as a part of general health checkup from January 2007 to December 2011 in the Health Screening and Promotion Center at Asan Medical Center, Seoul, Korea. Of them, 7129 (76.9%) individuals agreed to participate in this study. Detailed design, inclusion and exclusion criteria have been published previously.¹¹⁾ In summary, exclusions were as follows; prior angina or myocardial infarction, structure heart disease, prior cardiac intervention or surgery, ischemic electrocardiographic results, renal insufficiency (serum creatinine > 1.5 mg/dL) and insufficient checkup record. For this study, 1768 subjects who were on anti-hypertensive medication under diagnosis of hypertension were eliminated. Finally, 4666 subjects were enrolled (Fig. 1). The study was approved by the local Institutional Review Board of the Asan Medical Center, Seoul, Korea.

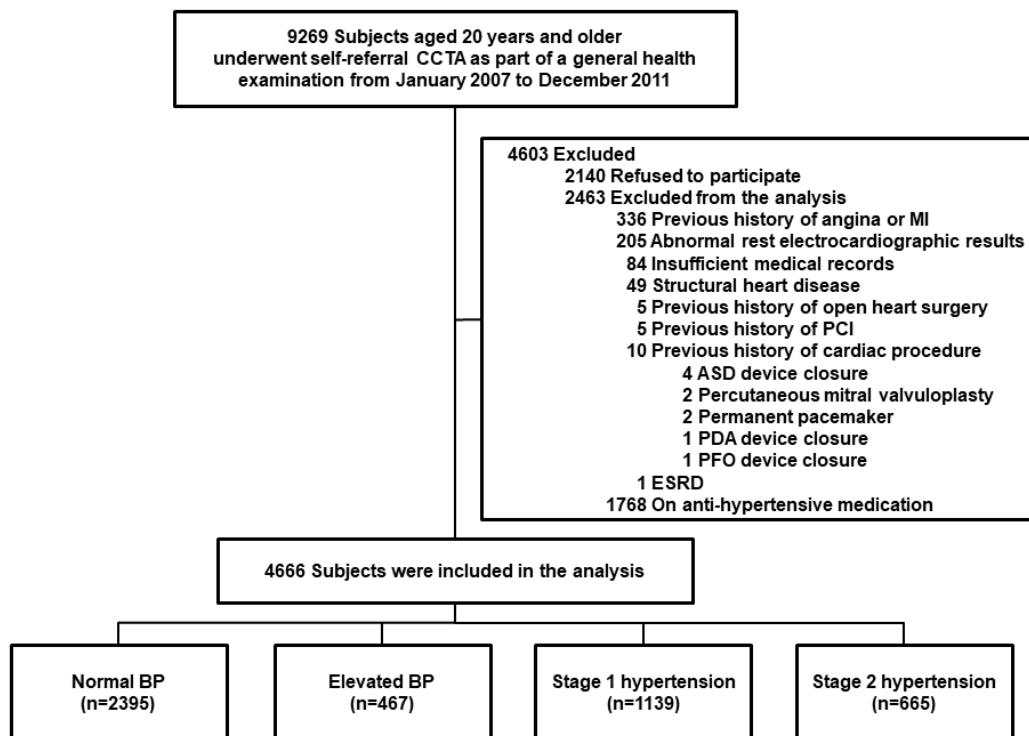


Fig. 1. Diagram of study flow

Definition

Hypertension was defined by ACC/AHA 2017 guideline; normal, systolic BP < 120 mm Hg and diastolic BP < 80 mm Hg; elevated, systolic BP \geq 120 mm Hg and diastolic BP < 80 mm Hg; stage 1 hypertension, systolic BP \geq 130 mm Hg or diastolic BP \geq 80 mm Hg, stage 2 hypertension, systolic BP \geq 140 mm Hg or diastolic BP \geq 90 mm Hg. The BP measurement for all subjects was conducted on the right arm after a rest of \geq 5 minutes using automatic manometers in appropriate cuff size. Status of diabetes were classified into 3 groups; overt diabetes mellitus (fasting plasma glucose \geq 126 mg/dL or hemoglobin A1C levels \geq 6.5%), prediabetes (fasting plasma glucose 100 mg/dL to 125 mg/dL or hemoglobin A1C levels 5.7–6.4%), or normal blood glucose. Hyperlipidemia was defined as total cholesterol \geq 240 mg/dL or on anti-hyperlipidemic treatment. If the subjects have first-degree relative diagnosed with CAD at any age, they were regarded to have family history of CAD. The 10-year cardiovascular risk of individuals in the study was estimated by Framingham risk score calculation.¹²⁾

CCTA Acquisition and Measurements

CCTA was performed using either single-source 64-slice CT (LightSpeed VCT, GE, Milwaukee, WI, USA) or dual-source CT (Somatom Definition, Siemens, Erlangen, Germany). The detailed protocol of CCTA was published previously. All CCTA images were analyzed by experienced cardiovascular radiologists using a dedicated workstation (Advantage Workstation, GE; or Volume Wizard, Siemens). The 16-segment coronary artery tree model was used in concordance with the guidelines of the Society of Cardiovascular Computed Tomography. The categorization of coronary artery calcium (CAC) score was as follows; 0, 1 – 10, 11 – 100, 101 – 400, > 400. Atherosclerotic plaque was defined as structures > 1 mm² within and/or adjacent to the vessel lumen, which is separated from the lumen or surrounding tissue. Non-calcified plaque was defined as a plaque not containing any calcium. Calcified plaque was defined as a plaque composed of calcium > 50% of the plaque area (density > 130 HU). Mixed plaque was defined as a plaque composed of calcium < 50%. The degree of stenosis in coronary segment was determined by comparing maximal stenosis site and

proximal or distal reference site. Stenosis $\geq 50\%$ was defined as significant. The overall plaque burden was assessed by calculating modified Duke prognostic scores, segment stenosis scores (SSS), and segment involvement scores (SIS).

Statistical Analysis

Categorical variables were reported as numbers with percentages and compared using Pearson's chi-square test. Continuous variables were reported as means with standard deviations and compared using one-way analysis of variance tests. Logistic regression model was used to adjust potential confounders for different outcomes. Clinically relevant variables were selected as potential risk-adjusting variables and input into the multivariable model for estimating the independent effect of BP groups. These covariates included age, sex, body-mass index, smoking status, family history of CAD, LDL cholesterol, total triglyceride, high density lipoprotein (HDL) cholesterol, serum creatinine, and high sensitivity C-reactive protein (hsCRP). In addition, generalized additive model was used to visualize continuous effect of systolic or diastolic BP on the risk for atherosclerotic coronary plaque with same confounders used in logistic regression model. All reported P values are two-sided and any less than 0.05 was considered statistically significant. All statistical analyses were performed with the use of the R software version 3.5.3.

RESULTS

Baseline characteristics

The mean age of study subjects was 52.6 ± 7.3 years and 3311 (71.0%) were men. According to the blood pressure category defined by 2017 ACC/AHA guideline, the individuals were categorized into 4 groups; normal, 2395 (51.3%); elevated, 467 (10.0%); stage 1 hypertension, 1139 (24.4%); and stage 2 hypertension, 665 (14.2%). The baseline characteristics of 4 groups are detailed in Table 1. Most risk factors and comorbid disease were tended to be common in the group with higher blood pressure level. Framingham risk score also increased as the level of BP category increases.

CCTA result

Table 2 shows CCTA result according to 4 groups. CAC score was highest in stage 2 hypertension, and higher also in elevated and stage 1 hypertension group than normal. The incidence of any atherosclerotic plaque showed linear pattern in concordance with increasing blood pressure groups. All types of plaque characteristics were common in hypertension groups, but the increments were prominent in non-calcified and mixed plaque. Overall plaque burden index, modified Duke prognostic score, SIS, and SSS showed also gradual relationship with the increasing BP categories. Significant stenosis > 50% was found more in higher BP groups.

After multivariate adjustment, stage 1 and 2 hypertensions were significantly associated with the presence of atherosclerotic plaque (adjusted odds ratio [OR], 1.38 [1.17 – 1.63]; $P = 0.0001$ and adjusted OR, 1.66 [1.36 – 2.03]; $P < 0.0001$) when compared to normal group. (Table 3) In analyses according to the characteristics of plaque morphology, non-calcified plaque and mixed plaque had positive association with both hypertension groups. Calcified plaque was not related at any stage of hypertension. Significant stenosis was found to be significantly higher only in stage 2 hypertension, but not in stage 1 hypertension. Elevated group did not have any significant association with all positive CCTA findings when compared to normal group.

Table 1. Baseline characteristics

	Normal (N=2395)	Elevated (N=467)	Hypertension		P
			Stage 1 (N=1139)	Stage 2 (N=665)	
Age	52.0 ± 7.1	53.3 ± 7.8	53.2 ± 7.0	53.0 ± 7.8	<0.001
Men	1461 (61.0)	339 (72.6)	948 (83.2)	563 (84.7)	<0.001
Weight, kg	65.0 ± 10.5	69.4 ± 10.8	70.8 ± 10.4	72.3 ± 10.7	<0.001
Height, cm	166.0 ± 7.9	167.4 ± 8.0	168.3 ± 7.2	168.6 ± 7.4	<0.001
BMI, kg/m ²	23.5 ± 2.7	24.7 ± 2.6	24.9 ± 2.8	25.3 ± 2.8	<0.001
Waist circumference, cm	82.4 ± 7.8	86.0 ± 7.5	86.8 ± 7.7	88.1 ± 7.7	<0.001
Systolic blood pressure, mmHg	108.9 ± 6.7	123.3 ± 2.7	126.1 ± 6.7	136.5 ± 12.3	<0.001
Diastolic blood pressure, mmHg	68.4 ± 6.4	74.8 ± 3.8	83.0 ± 3.7	90.2 ± 9.2	<0.001
Smoking					<0.001
Non-smoker	1106 (46.2)	176 (37.7)	354 (31.1)	195 (29.3)	
Current smoker	572 (23.9)	103 (22.1)	311 (27.3)	175 (26.3)	
Ex-smoker	717 (29.9)	188 (40.3)	474 (41.6)	295 (44.4)	
Diabetes type					<0.001
Non-diabetic	1102 (46.0)	153 (32.8)	328 (28.8)	181 (27.2)	
Prediabetes	1032 (43.1)	239 (51.2)	637 (55.9)	346 (52.0)	
Overt diabetes	261 (10.9)	75 (16.1)	174 (15.3)	138 (20.8)	
Dyslipidemia	639 (26.7)	147 (31.5)	351 (30.8)	232 (34.9)	<0.001
Previous stroke	5 (0.2)	2 (0.4)	8 (0.7)	5 (0.8)	0.096
Family history of CAD	371 (15.5)	70 (15.0)	168 (14.7)	106 (15.9)	0.902
Total cholesterol, mg/dL	196.2 ± 32.8	200.6 ± 35.1	201.6 ± 34.2	201.6 ± 34.5	<0.001
Triglyceride, mg/dL	115.8 ± 69.5	135.0 ± 78.4	144.6 ± 90.9	153.9 ± 111.9	<0.001
HDL cholesterol, mg/dL	55.6 ± 14.6	53.4 ± 13.1	52.7 ± 12.8	51.6 ± 12.5	<0.001

LDL cholesterol, mg/dL	122.2 ± 28.6	126.2 ± 30.5	126.1 ± 30.4	126.5 ± 29.4	<0.001
Fasting glucose, mg/dL	100.1 ± 17.4	105.6 ± 20.0	106.6 ± 22.9	106.8 ± 20.7	<0.001
HbA1c, %	5.6 ± 0.7	5.8 ± 0.8	5.8 ± 0.8	5.8 ± 0.8	<0.001
Serum creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.1	<0.001
hsCRP > 2.0 mg/dL	13 (0.5)	4 (0.9)	15 (1.3)	6 (0.9)	0.121
Framingham risk score, %	5.6 ± 4.4	8.0 ± 5.1	8.9 ± 5.0	10.5 ± 6.1	<0.001
Framingham risk score (category)					<0.001
< 10%	2038 (85.1)	327 (70.0)	753 (66.1)	365 (54.9)	
10 - 20 %	336 (14.0)	127 (27.2)	348 (30.6)	249 (37.4)	
> 20%	21 (0.9)	13 (2.8)	38 (3.3)	51 (7.7)	

Table 2. CT findings

	Normal (N=2395)	Elevated (N=467)	Hypertension		P
			Stage 1 (N=1139)	Stage 2 (N=665)	
Coronary artery calcium score	16.4 ± 77.9	35.4 ± 140.3	33.0 ± 109.4	45.9 ± 153.3	<0.001
Coronary artery calcium score category					<0.001
0	1874 (78.5)	319 (68.5)	731 (64.5)	395 (59.6)	
1 - 10	167 (7.0)	30 (6.4)	111 (9.8)	85 (12.8)	
11 - 101	256 (10.7)	78 (16.7)	189 (16.7)	114 (17.2)	
101 - 400	71 (3.0)	31 (6.7)	86 (7.6)	50 (7.5)	
> 400	20 (0.8)	8 (1.7)	16 (1.4)	19 (2.9)	
Atherosclerotic plaque	656 (27.4)	169 (36.2)	491 (43.1)	316 (47.5)	<0.001
Plaque characteristics type					
Non-calcified plaque	277 (11.6)	68 (14.6)	226 (19.8)	153 (23.0)	<0.001
Mixed plaque	112 (4.7)	29 (6.2)	110 (9.7)	60 (9.0)	<0.001
Calcified plaque	428 (17.9)	115 (24.6)	301 (26.4)	191 (28.7)	<0.001
Segment involvement score	0.6 ± 1.3	0.9 ± 1.5	1.0 ± 1.6	1.1 ± 1.6	<0.001
Segment stenosis score	0.3 ± 1.3	0.4 ± 1.3	0.5 ± 1.7	0.7 ± 2.0	<0.001
Modified Duke prognostic score	1.1 ± 0.5	1.1 ± 0.5	1.2 ± 0.6	1.2 ± 0.7	<0.001
Any significant stenosis > 50%	91 (3.8)	30 (6.4)	76 (6.7)	67 (10.1)	<0.001

Table 3. The association of BP categories and CT findings

	Elevated		Hypertension			
	adjusted OR (95% CI)	P	Stage 1 adjusted OR (95% CI)	P	Stage 2 adjusted OR (95% CI)	P
Atherosclerotic plaque	1.13 (0.89 - 1.42)	0.3172	1.38 (1.17 - 1.63)	0.0001	1.66 (1.36 - 2.03)	<0.0001
Non-calcified plaque	1.02 (0.76 - 1.38)	0.8798	1.40 (1.14 - 1.72)	0.0012	1.66 (1.31 - 2.09)	<0.0001
Mixed plaque	1.01 (0.65 - 1.57)	0.9693	1.59 (1.19 - 2.12)	0.0019	1.39 (0.98 - 1.98)	0.0628
Calcified plaque	1.11 (0.86 - 1.44)	0.4116	1.11 (0.92 - 1.34)	0.2646	1.21 (0.97 - 1.51)	0.0857
Stenosis > 50%	1.25 (0.80 - 1.95)	0.3247	1.21 (0.87 - 1.69)	0.2529	1.84 (1.29 - 2.61)	0.0007

Figure 2 shows the linear relationship of systolic and diastolic BP with the coronary atherosclerotic plaque in generalized additive model. Two BPs were significantly associated with any coronary plaque in linear relationship after multivariate adjustment.

The prevalence rate of 3 types of coronary plaque according to BP level and major baseline characteristics (age, sex, and diabetes) was illustrated in Figure 3. In overall, the incidences of atherosclerotic plaques were gradually higher in higher BP groups combined with older age, men, or the presence of diabetes.

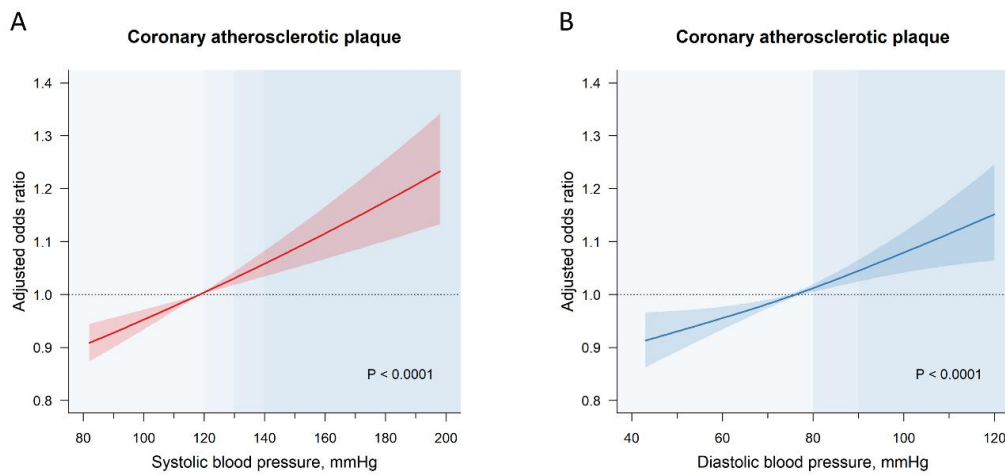


Fig. 2. The linear relationship of systolic and diastolic BP.

A, multiple risk adjusted odds ratio for coronary plaque and continuous systolic BP; B, multiple risk adjusted odds ratio for coronary plaque and continuous diastolic BP

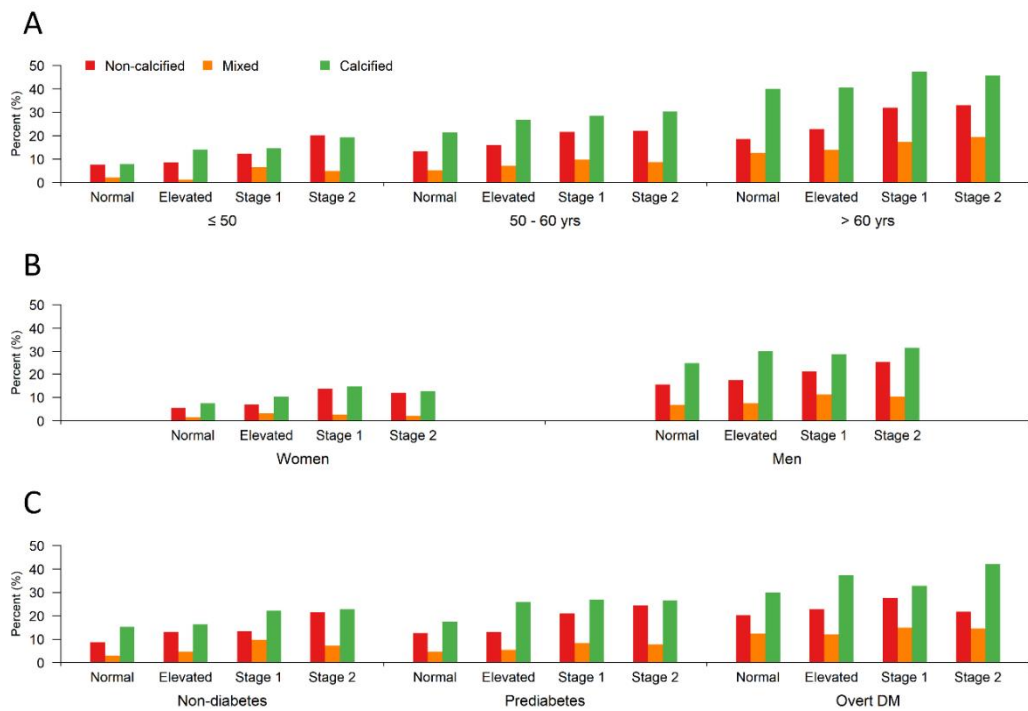


Fig. 3. Incidence of different types of coronary plaque according to BP and other clinical factors.

A, coronary plaque incidence according to BP category and age; B, coronary plaque incidence according to BP category and sex; C, coronary plaque incidence according to BP category and diabetes state

DISCUSSION

This study sought to describe the relationship of atherosclerotic plaque, and luminal stenosis detected by CCTA with newly revised hypertension criteria of ACC/AHA 2017 guideline. The main findings of this study are as follows; 1) atherosclerotic plaque, especially non-calcified and mixed plaque, was associated with stage 1 and 2 hypertensions. 2) The rate of significant stenosis > 50% was found to be higher in stage 2 hypertension, but not in stage 1 hypertension. 3) Linear relationship was observed between systolic/diastolic BP and atherosclerotic plaque.

The definition of hypertension had changed in the past, and it has not changed in the last two decades.⁶⁾ After releases of the most recent ACC/AHA and ESC/ESH guidelines,^{7,9)} there is ongoing issue about the patients in discrepancy between the two guidelines. It has become important to assess clinical aspects, long-term prognosis, and therapeutic benefit in the population categorized into stage 1 hypertension in ACC/AHA guideline (high normal or normal in category of ESC/ESH guideline). And this changed diagnosis criteria can also affect increased hospital visit, medical cost, and possible complications.

Our study demonstrated an independent and direct link between stage 1 hypertension and asymptomatic atherosclerotic plaque detected by CCTA. There are large evidences that prehypertension was related with adverse clinical outcomes. Blood pressure is in linear relationship with cardiovascular events above level at systolic/diastolic BP of 115/75 mmHg.¹³⁾ And prehypertension, formerly defined as being in the range of systolic BP 120 – 139 mmHg or diastolic BP 80 – 89 mmHg, also increased CAD and stroke from a meta-analysis.¹⁴⁾ The studies investigated the association of prehypertension and subclinical atherosclerosis was relatively small. A previous study reported grade-response relationship between blood pressure and subclinical atherosclerosis, and the prevalence of coronary plaque in prehypertension was significantly high.¹⁵⁾ Another study demonstrated higher CAC score in prehypertension, but also significant change in CAC score progression in prehypertension.¹⁶⁾ However, the risk for subclinical coronary atherosclerosis was different between stage 1 hypertension and elevated BP group from our study. Interestingly, elevated BP group below the threshold of hypertension diagnosis was not associated with any kind of positive CT findings after multiple risk adjustment. Considering that the stage 1 hypertension and elevated BP group was formerly categorized into the same group named prehypertension in JNC 7

definition, our finding advocates the most recent ACC/AHA guideline differentiating those two groups with respect to the asymptomatic coronary atherosclerosis.

The previous studies evaluated the relationship between BP and subclinical atherosclerosis by assessing mostly CAC score on non-enhanced CT.¹⁷⁻¹⁹⁾ The elevated BP and stage 1 hypertension defined by ACC/AHA 2017 guideline were known to increase CAC score in healthy population.¹⁹⁾ However, about a third of total plaques were non-calcified plaque according to the result of our study, even in elevated BP or stage 1 hypertension group. Even though quantification of coronary artery calcium (CAC) has been a reliable method for predicting adverse cardiovascular outcomes, noncalcified and mixed plaque appear to contain higher risk than fully calcified plaque.²⁰⁾ From the result of our study, CCTA may be a feasible option for the patients who are at increased risk of cardiovascular disease, such as stage 1 hypertension. However, because CCTA accompanies with radiation exposure, radio contrast, and high medical costs, the application of the test must be individualized for each patient.

Limitations

This study has several limitations. First, this study was a cross-sectional investigation, a causal relationship cannot be established from our findings. However, blood pressure is one of the risk factors for coronary atherosclerosis from lots of evidence, our study can conclude that stage 1 hypertension is independent risk for subclinical coronary atherosclerosis. Second, participation of study subjects was conducted at a health care department in single center. There must have potential selection bias in study enrollment. Third, even though there was a relationship between stage 1 hypertension and subclinical coronary atherosclerosis, this result cannot be interpreted directly as better outcome of anti-hypertensive treatment in this group. Finally, although CCTA has been performed voluntarily, the application of CCTA in a healthy population cannot be justified in the current guidance.

CONCLUSIONS

The stage 1 hypertension defined by ACC/AHA 2019 guideline (systolic BP 130 – 139 mmHg, diastolic BP 80 – 89 mmHg) was independently associated with subclinical coronary atherosclerosis. On the other hand, elevated BP was not independently associated with any findings in CCTA. Our study supports the most recent ACC/AHA hypertension guideline in terms of asymptomatic coronary atherosclerosis, which is closely linked to future cardiovascular events.

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국문 요약

연구배경

2017년 ACC/AHA 가이드라인에 의해 정의된 1 단계 고혈압과 관상동맥 CT 를 통해 평가된 무증상 관상동맥 죽상경화증의 관련성에 대한 연구는 부족한 실정이다.

연구방법

건강검진으로 관상동맥 CT 를 시행 받은 총 4666 명의 환자들이 이번 연구에 등록되었다. 고혈압은 2017년 ACC/AHA 가이드라인에 의해 정의되었다. 관상동맥 죽상반의 여부와 그 성상, 관상동맥칼슘점수, 그리고 혈관 내경이 50%이상 좁아져 있는 유의미한 협착이 평가되었다.

연구결과

연구대상자들의 평균나이는 52.6 ± 7.3 년이었고, 3311 명 (71.0%) 이 남성이었다. 대상자들은 다음과 같은 4 개의 군으로 분류되었다; 정상: 2395 명 (51.3%), 상승된 혈압: 467 명 (10.0%), 1 단계 고혈압: 1139 명 (24.4%), 2 단계 고혈압: 665 명 (14.2%). CT 결과에서는 혈압이 높은 군에 속할수록 관상동맥칼슘점수, 모든 종류의 관상동맥 죽상반, 유의미한 협착이 증가하는 경향을 보였다. 다변량 로지스틱 회귀분석에서는 정상과 비교하였을 때 1 단계 고혈압과 2 단계 고혈압이 관상동맥 죽상반, 특히 비칼슘성과 혼합형 죽상반과 유의하게 연관이 있었다 (보정교차비, 1.38 [1.17 – 1.63], $P = 0.0001$; 보정교차비 1.66 [1.36 – 2.03], $P < 0.0001$). 유의한 협착은 2 단계 고혈압에서만 유의하게 높았고 1 단계에서는 차이를 보이지 않았다. 상승된 혈압군은 어떤 관상동맥 CT 결과와도 연관성이 없었다. 수축기 혈압과 이완기 혈압 모두 연속된 값에서 관상동맥 죽상반과의 위험과 선형관계를 보여주었다.

연구결론

2017년 ACC/AHA 에 의해 정의된 1 단계 고혈압 (수축기 130 – 139 mmHg 또는 이완기 80 – 90 mmHg)은 무증상 관상동맥 죽상경화증과 독립적인 연관성이 있었다.

중심단어: 고혈압, 관상동맥 죽상경화증, 관상동맥 CT