Insufficient blood pressure control is independently associated with increased arterial stiffness

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Abstract

Hypertension is a risk factor for atherosclerosis. Achieving the therapeutic target value of blood pressure (BP) prevents the onset of cardiovascular events; however, it is not clear how antihypertensive drug use and BP control status relate to arterial stiffness. The purpose of this study is to investigate the relationship between BP control status with or without antihypertensive drugs and arterial stiffness. Nine hundred eighty individuals (mean age: 68±11 years) who participated in a community-based cohort study were enrolled. Arterial stiffness was evaluated using the cardio-ankle vascular index (CAVI). Higher BP was defined as a systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg. Participants were divided into four groups: normal, non higher BP without antihypertensive drugs (n=421); untreated, higher BP without antihypertensive drugs (n=174); good control, non higher BP with antihypertensive drugs (n=209); and poor control, higher BP with antihypertensive drugs (n=176). In multivariable logistic analysis adjusted for age, sex, dyslipidemia and diabetes mellitus medication use, obesity, smoking, alcohol drinking, and heart rate at the CAVI measurement for a high CAVI—using a borderline cutoff value of 8.0—the other three groups were significantly associated with a high CAVI when compared with the normal group. By contrast, multivariable logistic analysis of a high CAVI using an abnormal cutoff value of 9.0 demonstrated that the poor control and untreated groups were significantly associated with a high CAVI, whereas the good control group was not. In conclusion, even with antihypertensive drugs, poor BP control is independently associated with a high CAVI.

Keywords: Antihypertensive agents, Blood pressure, Risk factors, Vascular stiffness

Introduction

Cardiovascular diseases (CVDs), such as ischemic heart disease and stroke, are the leading causes of death worldwide, accounting for one-third of all deaths. The number of deaths from CVDs continues to increase [1]; therefore, it is necessary to evaluate the progression of atherosclerosis at an early stage and prevent the incidence of CVDs. Hypertension is one of the greatest risk factors for atherosclerosis [2,3], and as the level of blood pressure (BP) increases, so does the risk of CVD mortality [4]. The benefits of antihypertensive treatment for cardiovascular events have been reported in many studies [5,6,7]. Recently, the SPRINT study showed that strict BP control reduces cardiovascular events and is important to provide adequate antihypertensive therapy [8]. However, despite advances in antihypertensive drugs and the existence of treatment guidelines, the appropriate BP control rate remains at 50% [9]. Appropriate BP control can lead to a reduction in CVD events by achieving BP targets in individuals with inadequate control.

The early assessment of atherosclerosis and therapeutic intervention may also prevent the onset of CVD. The cardio-ankle vascular index (CAVI) is an arterial elasticity index that is independent of measured BP and can evaluate the degree of arterial stiffness [10,11]. The CAVI increases via the accumulation of atherosclerotic risk factors, such as diabetes mellitus, hypertension, smoking, high serum uric acid level, and sympathetic tone, in addition to irreversible factors, such as aging and sex [12-17]. Moreover, it was revealed that the CAVI was significantly associated with the presence and severity of coronary atherosclerosis [18] and could predict cardiovascular events in patients with atherosclerotic risk factors [19,20].

Although there is concern that inappropriate antihypertensive control may lead to the progression of atherosclerosis and development of CVD, it is unclear how antihypertensive drug use and BP control status relate to arterial stiffness. Therefore, the purpose of this study was to investigate the relationship between BP control status, including the presence or absence of antihypertensive drugs, and arterial function assessed by the CAVI in the general population.

Methods

Study Population

We enrolled 1,024 participants who were included in a community-based cohort study in Tarumizu city in 2019. Participants with atrial fibrillation on electrocardiogram (ECG) or a right or left ankle brachial index (ABI) <0.9 were excluded, as these factors may affect the reliability of CAVI measurements. Finally, 980 participants were analyzed in this study (**Figure 1**).

Before participating in this study, informed consent was obtained from all study participants. This study conformed to the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the Graduate School of Medical and Dental Sciences, Kagoshima University (Ref No. 170351).

Measurement of blood pressure and classification of participants

BP at the time of participation in the community-based cohort study was measured by the oscillometric method in the sitting position after 5 minutes at rest by experimental health nurses. In principle, BP was measured once; however, if the BP was above 180 mmHg (or higher than the usual BP value), it was remeasured, and the average was employed. Higher BP was defined as a systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, and participants were categorized into the following four groups: normal group: non higher BP without antihypertensive drugs; untreated group, higher BP without antihypertensive drugs; good control group, non higher BP with antihypertensive drugs; and poor control group, higher BP with antihypertensive drugs.

Measurement of the cardio-ankle vascular index

The CAVI was measured using a VaSera VS-1500 device (Fukuda Denshi, Tokyo, Japan). The cuffs were wrapped around the upper and lower extremities, and electrocardiographic electrodes were attached to the upper arm. A microphone was placed on the sternal angle to capture phonocardiographic signals. Participants rested on the bed in the supine position for 5 minutes, and the CAVI was automatically measured; the mean value of the left- and right-side CAVI was used for analysis. Cutoff values of 8.0 and 9.0 (<8.0 for normal, ≥8.0 and <9.0 for borderline, ≥9.0 for abnormal) were previously demonstrated for the CAVI [21] and were used as cutoff values in this study.

Determination of risk factors

Patient data, including alcohol consumption status (at least one day a week or none at all) and smoking history (current smoker, never smoker), were obtained through self-administered questionnaires. Information on medications for hypertension, dyslipidemia, and diabetes mellitus was acquired face-to-face by a specialized public health nurse; if the participants had taken their medication book, the book was used to conduct the survey. Body mass index (BMI) was calculated as body weight (kg) divided by the height squared (m), and we defined obesity as a BMI $\geq$25 kg/m^2.

Statistical analyses

Continuous variables are presented as the means and standard deviations or the medians and 25th and 75th percentiles, as appropriate. Categorical variables are expressed as the numbers of participants and proportions (percentages). Comparisons between the four groups were conducted using one-way analysis of variance for continuous variables and chi-square tests for categorical variables, with Bonferroni correction for post-hoc comparisons. The significance level for Bonferroni correction was set at $P < 0.008$.

CAVI values were divided into two groups, using 8.0 as the borderline or 9.0 as abnormal. Univariable and multivariable multinomial logistic regression analyses were used to determine which groups were related to a high CAVI. The normal group was used as the reference category. Multivariable logistic analyses adjusted for age, sex, dyslipidemia and diabetes mellitus medication use, obesity, smoking, alcohol drinking, and heart rate at the CAVI measurement were performed. $P < 0.05$ was set as the level of significance for all statistical analyses except Bonferroni correction, and all data analyses were performed using JMP Pro 15 (SAS Institute, Cary, NC, USA) for Mac.

Results

Participant's characteristics

The characteristics of the 980 participants are shown in Table 1, including 372 males (38%) and 609 females (62%); the mean age was 68±11 years. Participants were divided into four groups, with 421

(43%) in the normal group, 174 (18%) in the untreated group, 209 (21%) in the good control group, and 176 (18%) in the poor control group. The normal group was the youngest and exhibited the lowest BP and BMI values compared with the other three groups. The rates of receiving medications for dyslipidemia and diabetes mellitus in the normal or untreated group were lower than those in the good control or poor control group.

The mean CAVI in the normal group exhibited a substantially lower value than that in the other three groups (normal group: 8.3±1.1; untreated group: 8.8±1.4; good control group: 9.0±1.2; poor control group: 9.1±1.1) and was lower in the untreated group than in the groups treated with antihypertensive drugs.

Multinominal logistic analysis of a high CAVI using a borderline cutoff value of 8.0

Figure 2 shows the univariable logistic analysis of a high CAVI using a borderline cutoff value of 8.0. When the normal group was used as a reference, the untreated group was significantly associated with a high CAVI (odds ratio: 2.12; P=0.0001). Additionally, the two groups with antihypertensive drug use had high odds ratios, while the poor control group had an even higher odds ratio (good control group: odds ratio 4.43, P<0.0001; poor control group: odds ratio 5.26, P<0.0001).

Figure 3 shows the results of the multivariable logistic analysis of a high CAVI adjusted for age, sex, dyslipidemia and diabetes mellitus medication use, obesity, smoking, alcohol drinking, and heart rate at the CAVI measurement. When the normal group was used as a reference, the other three groups were significantly associated with a high CAVI, with the highest odds ratio observed in the poor control group (untreated group, odds ratio: 1.83, P=0.0104; good control group, odds ratio: 1.86, P=0.0175; poor control group, odds ratio: 2.67, P=0.0005).

Multinominal logistic analysis of a high CAVI using an abnormal cutoff value of 9.0

Figure 4 shows the univariable logistic analysis of a high CAVI using an abnormal cutoff value of 9.0. When the normal group was used as a reference, the other three groups were all significantly associated with a high CAVI (untreated group, odds ratio: 2.25, P<0.0001; good control group, odds ratio: 3.10, P<0.0001; poor control group, odds ratio: 3.56, P<0.0001).

Figure 5 shows the multivariable logistic analysis of a high CAVI adjusted for age, sex, dyslipidemia and diabetes mellitus medication use, obesity, smoking, alcohol drinking, and heart rate at the CAVI measurement. When the normal group was used as a reference, both the untreated and poor control groups were significantly associated with a high CAVI (untreated group, odds ratio: 1.81, P=0.0081; poor control group, odds ratio: 1.91, P=0.0048). By contrast, the good control group was found to have no significant association with a high CAVI.

Discussion

In this study, we investigated the relationship between BP control status with or without antihypertensive drugs and arterial stiffness assessed using the CAVI. The CAVI in the normal group was substantially lower than that in the other groups. In the multivariable logistic analysis of a high CAVI using a borderline cutoff value of 8.0—adjusted for age, sex, dyslipidemia and diabetes mellitus medication use, obesity, smoking, alcohol drinking, and heart rate at the CAVI measurement—compared with the normal group, the other three groups were significantly associated with a higher CAVI. By contrast, the multivariable logistic analysis of a high CAVI using an abnormal cutoff value of 9.0 demonstrated that compared with the normal group, the poor control and untreated groups (not the good control group) were significantly associated with a high CAVI.

Hypertension is a risk factor for the progression of atherosclerosis, resulting in the development of CVDs and ultimately leading to a poor life prognosis [22,23]. Appropriate BP control has been shown to reduce the incidence of these diseases and improve prognosis; therefore, the therapeutic goal of treating hypertension is to prevent the development of cardiovascular disease caused by persistent hypertension, as well as to improve life expectancy. To achieve this goal, appropriate BP control is essential; however, there are patients with higher BP who remain untreated or whose BP does not reach the target level, despite taking antihypertensive drugs.

In this study, we used the CAVI, a useful index for the noninvasive evaluation of arterial stiffness [11]. An elevated CAVI is associated with the occurrence of cardiovascular events [19,24]. Various studies have reported cutoff values for the development of atherosclerosis and CV events for the CAVI. The CAVI cutoff value for predicting coronary artery stenosis $\geq$ 50% was 8.0 or greater [25]. Early

intervention for risk factors such as hypertension, dyslipidemia, and diabetes mellitus is necessary to prevent or inhibit the progression of atherosclerosis. We considered that a borderline cutoff value (8≥) was necessary to motivate patients to improve their treatment adherence and lifestyle. Furthermore, a CAVI of 9.0 or higher predicts future total cardiovascular events in asymptomatic patients with type 2 diabetes mellitus [26]. In patients with acute coronary syndrome, a CAVI of 8.325 or higher was a predictor of cardiovascular events [27]. Moreover, when patients with metabolic syndrome were divided into quartiles based on the CAVI, the occurrence of events increased with increasing quartile [quartile 3 (9.2-10.08) and quartile 4 (≥ 10.09)], and the CAVI value of the event-free group (9.19±1.55) was significantly lower than that of the incident event group (9.86±2.83) [20]. To evaluate the usefulness of the CAVI for predicting CVD incidence and risk stratification, it would be useful to set the cutoff value at 9.0. Therefore, it was previously reported that a CAVI below 8.0 is considered normal, 8.0–9.0 is borderline, and above 9.0 is abnormal [18]; thus, we used two cutoff points in this study. The untreated and poor control groups were associated with both a CAVI ≥8.0 and ≥9.0, whereas the good control group was associated with a CAVI ≥8.0 but not ≥9.0. Our results suggest that while hypertension leads to increased arterial stiffness, appropriate BP control can inhibit its progression. A meta-analysis investigating the relationship between the level of BP control through antihypertensive drugs and the prevention of CVD has shown that lowering BP to levels below those recommended by current guidelines reduces the risk of CVD [28]. Increased arterial stiffness causes myocardial remodeling, including hypertrophy and fibroses of the myocardial interstitium, as well as coronary artery endothelial damage. Appropriate BP control may therefore improve arterial stiffness and thereby prevent CVD.

Among the 559 participants with a higher BP in this study, 176 (32%) had a higher BP despite taking antihypertensive drugs, 174 (31%) had a higher BP but did not receive treatment, and only 209 (37%) had controlled BP with antihypertensive drugs. According to the Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2019) [9], 31 million (72%) of the 43 million patients with hypertension in 2017 had uncontrolled BP; among them, it was estimated that 14 million (33%) had undiagnosed hypertension, 4.5 million (10%) were diagnosed but untreated, and 12.5

million (29%) were treated but had uncontrolled hypertension. To prevent CVD caused by hypertension, it is necessary to reduce the number of individuals with poorly controlled hypertension. To improve BP control, medication adherence needs to be improved. Medication adherence has been shown to be associated with not only BP control [29] but also the development of CVD [30]. Additionally, clinical inertia has recently been highlighted as a factor in the inadequacy of hypertension control [31,32]. Clinical inertia may sustain inadequate BP control, which in turn may adversely affect life expectancy and the development of CVD. Educational interventions for patients and primary care providers are therefore important to solve these problems [33]. On the other hand, it has been reported that elevated arterial stiffness leads to difficulty in controlling BP [34]. In this study, the poor control group was associated with an increased CAVI. Increased arterial stiffness may have led to inadequate BP control due to the lack of efficacy of the antihypertensive drugs. However, because this was a cross-sectional study, it was not possible to clarify whether poor BP control causes increased arterial stiffness or whether the progression of arterial stiffness makes hypertension intractable. In any case, appropriate BP control before the development of atherosclerosis is necessary to prevent the development of CVD and to improve life prognosis.

Limitations

This study has several limitations. First, this was a cross-sectional study, and prospective longitudinal studies are needed to confirm whether changes in hypertension management can improve CAVI values. Second, since this study was conducted on health checkup participants, obtaining multiple BP measurements was difficult due to time constraints; thus, for most participants, BP was measured just once. However, multiple BP measurements should be used to obtain accurate BP information, and therefore, further research on this topic is desirable. Third, the type of antihypertensive medication and duration of hypertension were not known. The organ-protective effects of antihypertensive drug therapy have been reported to vary among antihypertensive drugs; in fact, even when BP is lowered by antihypertensive drugs, their effect on the CAVI differs according to the type of antihypertensive drug [35,36]. Therefore, it is necessary to investigate the effect of different types and numbers of antihypertensive drugs and durations of disease on CAVI values.

Perspective in Asia

The present study shows that appropriate antihypertensive control is associated with arterial stiffness, regardless of whether patients are taking antihypertensive medications. This result could be common not only in Japan and other Asian countries but also worldwide. In this study, arterial stiffness was assessed using the CAVI. Previously, carotid-femoral pulse wave velocity was used as an index of central arterial stiffness, while the CAVI is an indicator developed in Japan that evaluates arterial stiffness from central to peripheral arteries. There have been many reports on the usefulness of the CAVI from Asia, including Japan. We used an abnormal cutoff value of 9.0 and found that there was a significant association when BP was uncontrolled with medication use but not when BP was controlled. This is an important message from Asia that it is not enough to just provide patients with medications but that medication adjustments to achieve adequate BP control are significantly related to arterial function. In addition, the cutoff values were developed based on reports from Asia (Japan, Korea, China, and Taiwan), [18] whereas there are few reports from non-Asian countries showing cutoff values for the CAVI. Therefore, this study may lead to early lifestyle modification and medication adjustments to prevent atherosclerosis, especially among Asians, and thus reduce the occurrence of CVD events.

Conclusion

Poor BP control is independently associated with arterial stiffness, even with the use of antihypertensive drugs.

Conflicts of Interest

The authors declare no competing interests.

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Figure legends

Figure 1. Participant selection process flowchart

Figure 2. Univariable logistic analysis of a high CAVI (≥8.0)

CAVI, cardio-ankle vascular index; OR, odds ratio; CI, confidence interval

Figure 3. Multivariable logistic analysis of a high CAVI (≥8.0) adjusted for age, sex, dyslipidemia and diabetes mellitus medication use, obesity, smoking, alcohol drinking, and heart rate at the CAVI measurement

CAVI, cardio-ankle vascular index; OR, odds ratio; CI, confidence interval

Figure 4. Univariable logistic analysis of a high CAVI (≥9.0)

CAVI, cardio-ankle vascular index; OR, odds ratio; CI, confidence interval

Figure 5. Multivariable logistic analysis of a high CAVI (≥9.0) adjusted for age, sex, dyslipidemia and diabetes mellitus medication use, obesity, smoking, alcohol drinking, and heart rate at the CAVI measurement

CAVI, cardio-ankle vascular index; OR, odds ratio; CI, confidence interval

Point of view

Clinical relevance

Poor BP control is independently associated with arterial stiffness, even with the use of antihypertensive drugs.

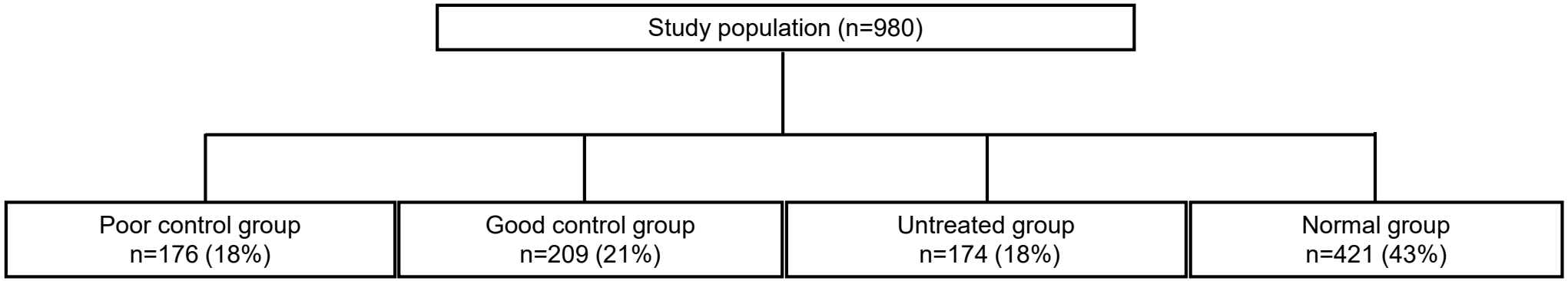
Future direction

The importance of appropriate blood pressure control is demonstrated by this study and will lead to lifestyle modifications and pharmacological adjustments for proper blood pressure control.

Considerations for the Asian population

This study could lead to early lifestyle modifications and medication adjustments to prevent atherosclerosis, especially among Asians.

The relationship between BP control status with or without antihypertensive drugs and arterial stiffness.



Multivariable logistic analysis of a high CAVI (≥8.0)

	OR (95% CI)	P-value
Nomal group	Reference	
Untreated group	1.83 (1.15-2.90)	0.0104
Good control group	1.86 (1.11-3.09)	0.0175
Poor control group	2.67 (1.53-4.66)	0.0005

Multivariable logistic analysis of a high CAVI (≥9.0)

	OR (95% CI)	P-value
Normal group	Reference	
Untreated group	1.81 (1.17-2.82)	0.0081
Good control group	1.40 (0.91-2.14)	0.1211
Poor control group	1.91 (1.22-2.99)	0.0048

Poor BP control is independently associated with arterial stiffness, even with the use of antihypertensive drugs.

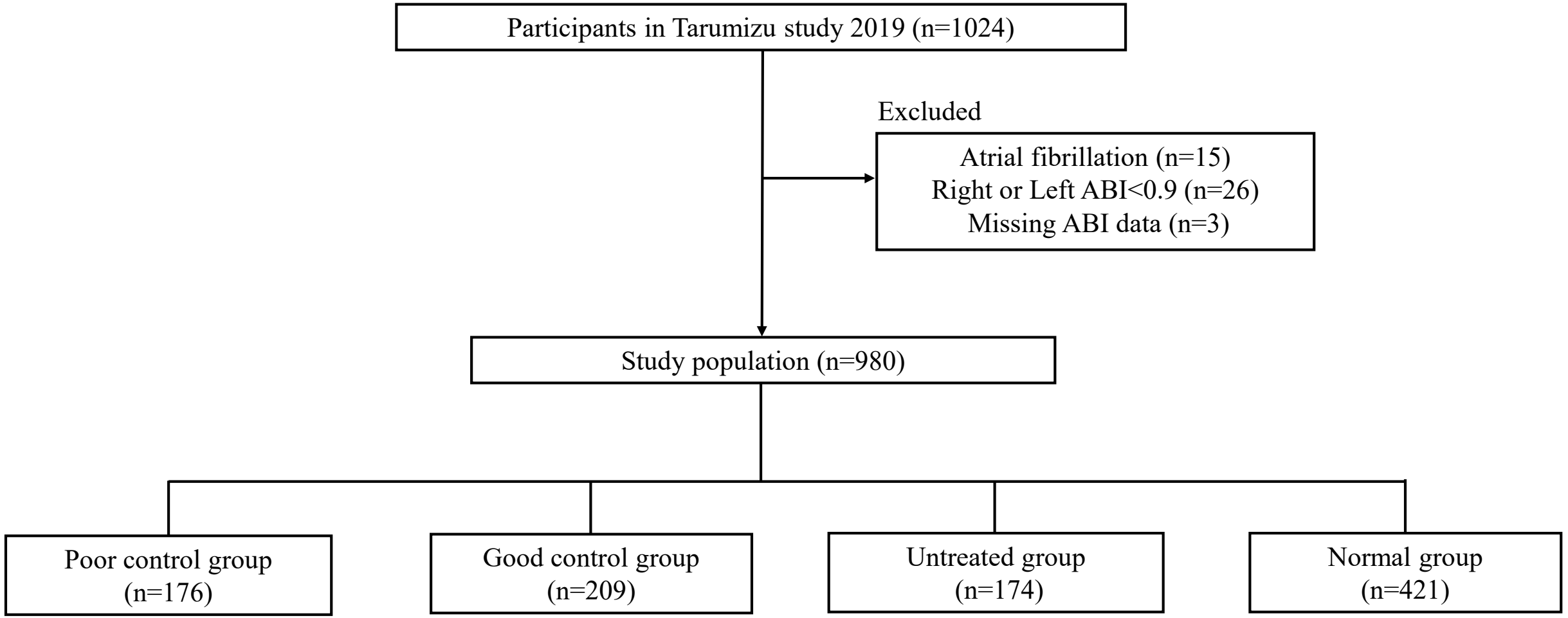

Participants in Tarumizu study 2019 (n=1024)
Excluded
Atrial fibrillation (n=15)
Right or Left ABI<0.9 (n=26)
Missing ABI data (n=3)
Study population (n=980)
Poor control group (n=176)
Good control group (n=209)
Untreated group (n=174)
Normal group (n=421)

Fig. 1

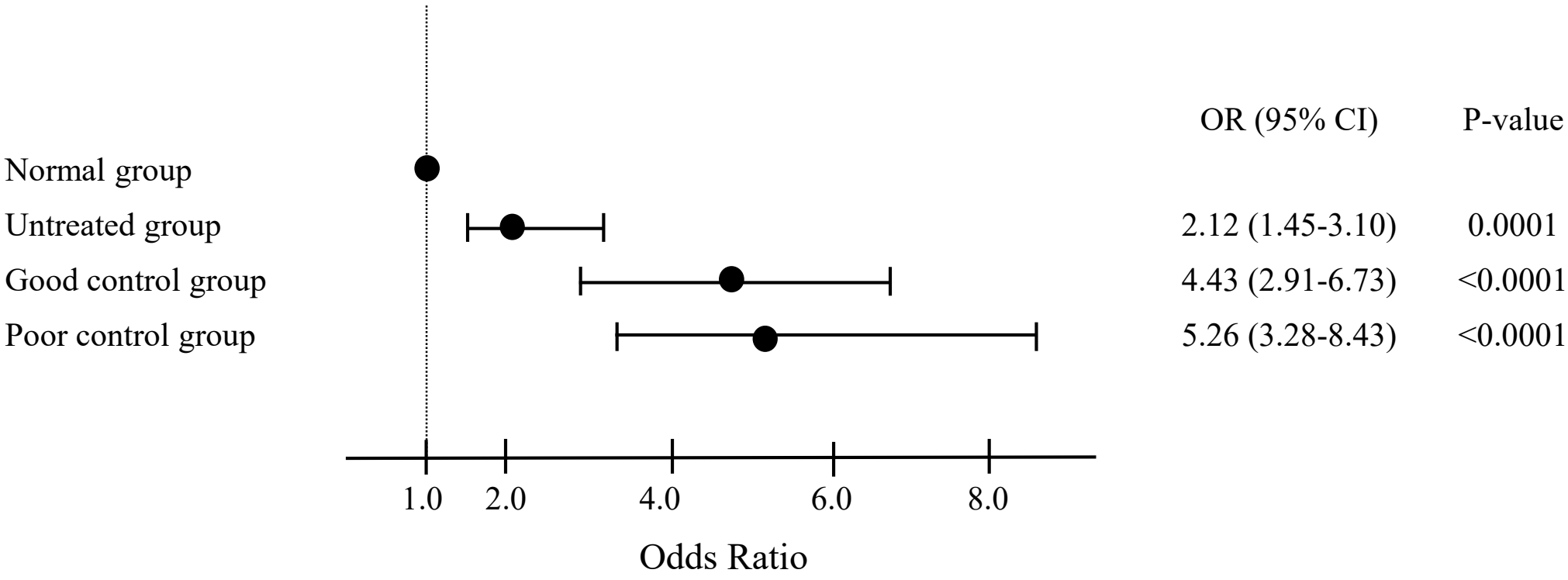

OR (95% CI)
P-value
Normal group
Untreated group
2.12 (1.45-3.10)
0.0001
Good control group
4.43 (2.91-6.73)
<0.0001
Poor control group
5.26 (3.28-8.43)
<0.0001
1.0
2.0
4.0
6.0
8.0
Odds Ratio

Fig. 2

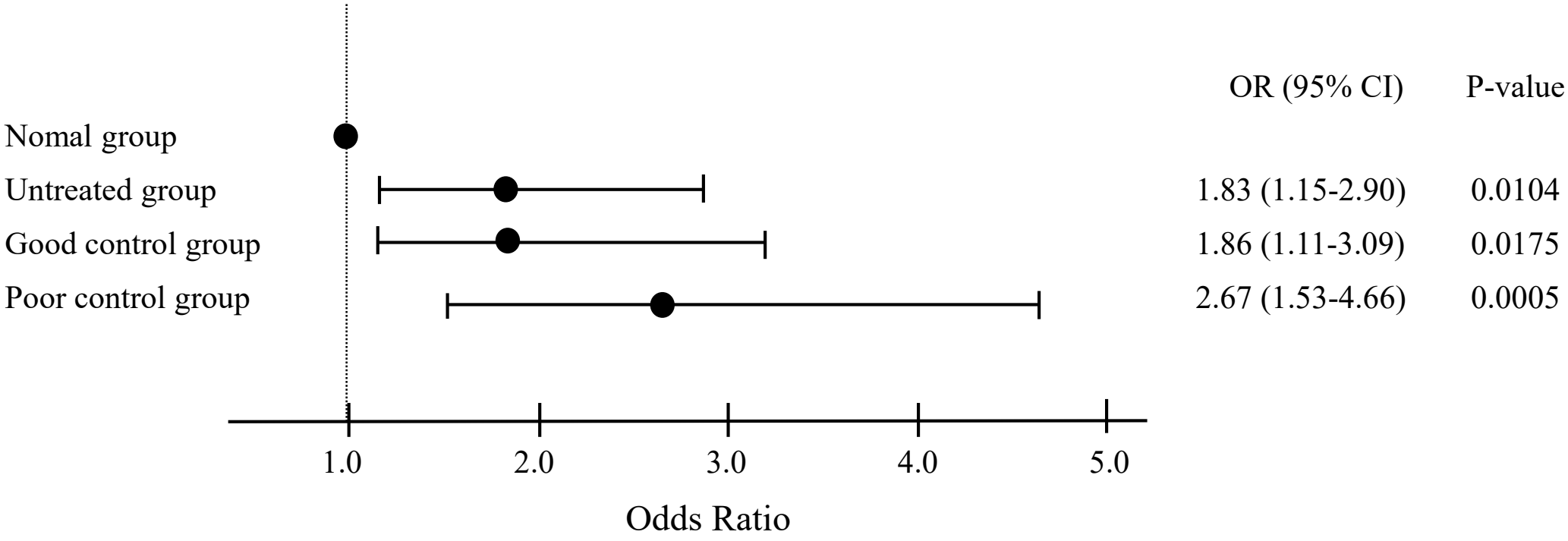

OR (95% CI)
P-value
Nomal group
Untreated group
1.83 (1.15-2.90)
0.0104
Good control group
1.86 (1.11-3.09)
0.0175
Poor control group
2.67 (1.53-4.66)
0.0005
1.0
2.0
3.0
4.0
5.0
Odds Ratio

Fig. 3

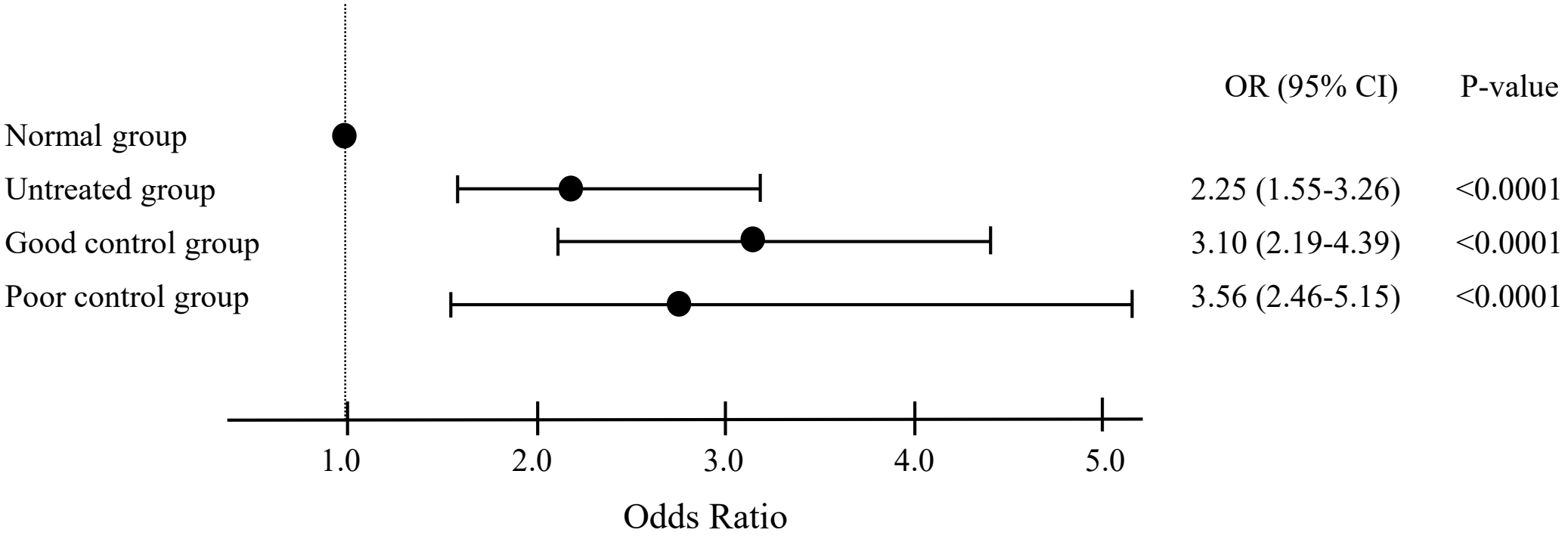

OR (95% CI)
P-value
Normal group
Untreated group
2.25 (1.55-3.26)
<0.0001
Good control group
3.10 (2.19-4.39)
<0.0001
Poor control group
3.56 (2.46-5.15)
<0.0001
1.0
2.0
3.0
4.0
5.0
Odds Ratio

Fig. 4

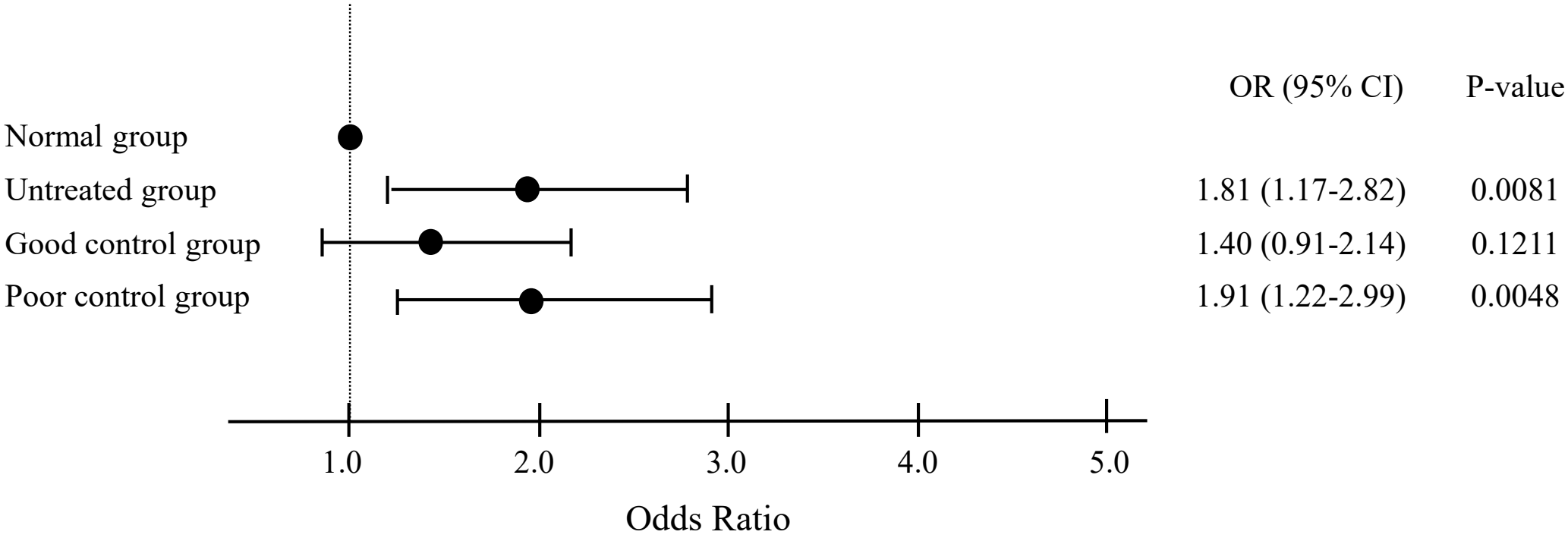

OR (95% CI)
P-value
Normal group
Untreated group
1.81 (1.17-2.82)
0.0081
Good control group
1.40 (0.91-2.14)
0.1211
Poor control group
1.91 (1.22-2.99)
0.0048
1.0
2.0
3.0
4.0
5.0
Odds Ratio

Fig. 5

Table 1. Characteristics of the four groups divided by the level of blood pressure and status of receiving antihypertensive drugs

	Normal group (n=421)	Untreated group (n=174)	Good control group (n=209)	Poor control group (n=176)	P value
Age (years)	64±11	67±11 $^{\#}$	73±9 $^{\#\#, **}$	73±9 $^{\#\#, **}$	<0.0001
Male / Female	134/287	73/101	92/117 $^{\#}$	73/103	0.0071
BMI (kg/m^2)	22.4±3.1	23.4±3.6 $^{\#}$	23.1±3.3 $^{\#\#}$	24.2±3.4 $^{\#\#}$	<0.0001
Systolic BP (mmHg)	121±12	149±12 $^{\#\#}$	126±9 $^{\#, **}$	151±11 $^{\#\#, +}$	<0.0001
Diastolic BP (mmHg)	73±8	87±10 $^{\#\#}$	73±9 **	84±11 $^{\#\#, +}$	<0.0001
Heart rate (bpm)	65.5±9.7	69.5±11.7 $^{\#\#}$	65.4±9.3 *	67.8±11.2	<0.0001
Alcohol drinking, n (%)	208 (49)	89 (51)	100 (48)	76 (43)	0.4514
Smoking, n (%)	110 (26)	53 (30)	78 (37) $^{\#}$	58 (33)	0.0309
Medications					
Antihypertensive drugs, n (%)	0 (0)	0 (0)	209 (100) $^{\#\#, **}$	176 (100) $^{\#\#, **}$	<0.0001
Lipid-lowering drugs, n (%)	58 (14)	23 (13)	63 (30) $^{\#\#, **}$	58 (33) $^{\#\#, **}$	<0.0001
Hypoglycemic drugs, n (%)	13 (3)	9 (5)	34 (16) $^{\#\#, *}$	26 (15) $^{\#\#, *}$	<0.0001
CAVI	8.3±1.1	8.8±1.4 $^{\#\#}$	9.0±1.2 $^{\#\#}$	9.1±1.1 $^{\#\#}$	<0.0001
CAVI ≥ 8.0, n (%)	230 (55)	125 (72) $^{\#\#}$	176 (84) $^{\#\#, *}$	152 (86) $^{\#\#, *}$	<0.0001

CAVI ≥ 9.0, n (%)	108 (26)	76 (44) [##]	108 (52) [##]	97 (55) [##]	<0.0001

Continuous variables are expressed as mean ± standard deviation.

BMI, Body mass index; BP, blood pressure; CAVI, cardio-ankle vascular index

[#] P<0.008, [##] P<0.0001 vs. control group; * P<0.008, ** P<0.0001 vs. untreated group; [+] P<0.0001 vs. good control group.