Hypertension

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Association Between Hypertension and Incident Infective Endocarditis

Gyu Bae Lee,* Koh Eun Shin,* Kyungdo Han, Ho-Sung Son, Jae-Seung Jung, Yang-Hyun Kim, Hee-Jung Kim

BACKGROUND: This study aimed to evaluate the association of hypertension with incident infective endocarditis (IE) by investigating the incidence of IE according to blood pressure levels using the National Health Insurance Service database.

METHODS: The data of 4 080 331 individuals linked to the health screening database in 2009 were retrieved (males, 55.08%; mean age, 47.12±14.13 years). From 2009 to 2018, the risk factors for the first episode of IE were investigated. Hypertension was categorized into normotension, prehypertension, hypertension, and hypertension with medication. The Cox proportional hazard model assessed the effect of blood pressure level during the health screening exam on incident IE.

RESULTS: During the 9-year follow-up, 812 (0.02%) participants were diagnosed with IE. The incidence rates of IE in the normotension, prehypertension, hypertension, and hypertension with medication groups were 0.9, 1.4, 2.6, and 6.0 per 100 000 person-years, respectively. Those with prehypertension, hypertension, and hypertension with medication were correlated with an increased risk of IE in a dose-response manner compared with the normotension group (hazard ratio, 1.33 [95% CI, 1.06–1.68]; hazard ratio, 1.98 [1.48–2.66]; hazard ratio, 2.56 [2.02–3.24], respectively, all $P<0.001$).

CONCLUSIONS: In a large national cohort study with an average follow-up of 9 years, increased blood pressure was identified as a risk factor for incident IE in a dose-dependent manner. Hypertension increases the public health care burden by acting as a risk factor for rare infective heart diseases. **(*Hypertension*. 2022;79:1466–1474. DOI: 10.1161/HYPERTENSIONAHA.122.19185.)** • **Supplemental Material**

Key Words: cardiovascular diseases ■ endocarditis ■ heart failure ■ hypertension ■ risk factors

Infective endocarditis (IE), a rare disease associated with significant morbidities such as heart failure, septic emboli, stroke, and organ failure, is associated with an in-hospital mortality rate of 20%.[1] The annual incidence of IE in developed countries has been known to be static at 3 to 7 cases per 100 000 individuals; however, recent reports have indicated an increase in its incidence.[2–6] Such findings call for an analysis of risk factors for IE, especially when prior IE, prosthetic valves, and congenital heart disease have been indicated as high-risk factors for IE.[7]

Hypertension is a widely recognized risk factor for cardiovascular disease, but the association between hypertension and IE is not established.[8] Higgins et al[9] estimated the long-term impact of blood pressure lowering on IE using Mendelian Randomization with UK Biobank cohort. They illustrated that reduction in systolic blood pressure results in lower incidence of chronic cardiovascular disease and infectious disease (IE and rheumatic heart disease). Previous researches mention hypertension as a risk factor for major adverse cardiac events following IE[10]; furthermore, hypertension has been more often identified with pulmonary valve IE in patients without IE risk factors.[11] Based on these limited findings, hypertension may contribute to the incidence of infectious disease involving the heart.

Considering the recent rise in the incidence of IE and the fact that little research has been conducted on the relationship between blood pressure levels and IE

Correspondence to: Yang-Hyun Kim, Department of Family Medicine, Korea University College of Medicine, 222, Korea-daero, Seongbuk-gu, Seoul, 02841, Korea, Email 9754031@korea.ac.kr or Hee-Jung Kim, Department of Thoracic and Cardiovascular Surgery, Korea University College of Medicine, 222, Korea-daero, Seongbuk-gu, Seoul, 02841, Korea, Email heejung440@hanmail.net
*G.B. Lee and K.E. Shin contributed equally.
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NOVELTY AND RELEVANCE

What Is New?

Those with prehypertension, hypertension, and hypertension with medication were correlated with an increased risk of infective endocarditis (IE) in a dose-response manner compared with normotension group

What is Relevant?

Risk factors for incident IE were not well understood, especially in relation to blood pressure. What is the association between hypertension and incident IE?

In a large national cohort study with an average follow-up of 9 years, hypertension was a risk factor for incident IE in a dose-dependent relationship.

Clinical/Pathophysiological Implications?

Hypertension was associated with increased risk of incident IE. Therefore, hypertension increases the public health care burden by acting as a risk factor for rare infectious diseases involving the heart.

Nonstandard Abbreviations and Acronyms

ACE	angiotensin-converting enzyme
ARB	angiotensin receptor blockers
DBP	Diastolic blood pressure
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
ICD	*International Classification of Disease*
IE	Infective endocarditis
LDL-C	low-density lipoprotein cholesterol
NHIS	National Health Insurance Service
SBP	Systolic blood pressure

incidence, we hypothesized that hypertension may serve as a risk factor for incident IE. Therefore, to understand this relationship that may explain the rise in IE cases worldwide, this study used a nationwide population database to analyze a cohort of 4 million participants, with up to 9 years of follow-up.

METHODS

Study Design and Ethics Statement

Because of the sensitive nature of the data collected for this study, requests to access the data set from qualified researchers trained in human subject confidentiality protocols may be sent to National Health Insurance Service at (https://nhiss.nhis.or.kr/). Details of this process and a provision guide are now available at (https://nhiss.nhis.or.kr/bd/ab/bdaba032eng.do.). The current retrospective study analyzed the incidence of IE in South Korea using nationwide population data, mainly focusing on the incidence of IE with respect to hypertension. The present study used general health check-up data from the National Health Insurance Service (NHIS), and no additional participants were enrolled. The analyses strictly obeyed the operating regulations of the NHIS. This study was approved by the Institutional Review Board of Korea University Anam Hospital (IRB-2021AN0153), and permission was granted to use the NHIS health check-up data (NHIS-2021-1-698). De-identified and anonymized data were used for the analyses, and the requirement for informed consent was waived.

Data Source

This study used the health screening data of the year 2009 from the NHIS. South Korea operates a centralized universal health insurance program, and insured citizens ≥40 years of age are required to biannually participate in the health check-up program of NHIS; conversely, the employed-individuals who are ≥20 years of age participate in annual check-ups. It is estimated that almost 97.0% of Koreans participate in this mandatory universal health check-up. The NHIS manages the centralized National Health Insurance program, which includes ≈50 million Koreans. The claimed data, composed of the NHIS health check-up program, includes information such as age, sex, insurer payment coverage, area of residence, medical utilization/transaction information, deductions, and claims data.

During the check-up, a certified examiner recorded the anthropometric measurements, including height (cm), weight (kg), waist circumference)(cm), systolic blood pressure (SBP; mm Hg), and diastolic blood pressure (DBP; mm Hg). For blood pressure measurements, certified examiners who received periodic trainings measured SBP and DBP of the participants and recorded the average BP value from 2 measurements. The examiners measured BP using sphygmomanometers or oscillometer devices after 5 minutes of rest.

Laboratory tests include fasting blood glucose (mg/dL), total cholesterol (mg/dL), LDL-C (low-density lipoprotein cholesterol; mg/dL), HDL-C (high-density lipoprotein cholesterol; mg/dL), triglycerides (mg/dL), aspartate aminotransferase (IU/L), alanine aminotransferase (IU/L), and serum creatinine (mg/dL). General health behaviours are investigated using self-completed questionnaires, including questions about alcohol consumption, smoking, and exercise. The Korean Association of Laboratory Quality Control evaluates the quality of the laboratory tests, and health check-ups are only provided at NHIS-certified hospitals. Details about the NHIS data set and the health check-up process have been described in previous publications.[12,13]

Definition of IE and High-Risk Group

IE was defined as patients who were admitted to hospitals with *International Classification of Disease* (ICD)-10 codes (I33.x,

ORIGINAL ARTICLE

I38.x, and I39.8). Of the patients with ICD codes for IE, only those who were hospitalized for >14 days or died within 14 days were included in the analyses, and anyone with ≤14 days of hospitalization without death was excluded (see Table S1). The high-risk group of IE was designated to the patients with ICD codes or procedure codes for congenital heart disease, intracardiac device, and heart valve prosthesis (see Table S1 for specific procedure codes).

Participants

First, the health screening check-ups including blood pressure measurement were conducted in 4 million participants in the year of 2009. Second, the participants younger than 20 years and those with missing data (n=152 775) were excluded. Additionally, the participants with prior diagnosis of IE were excluded from the analysis (washout; n=1233) since the current study focused on the incident IE. Third, because the NHIS database carries the information on admission, outpatient, and medication prescriptions of Korean population and we then searched the NHIS database for the occurrence of IE after the year 2009 using the ICD codes (mean follow-up duration of 9.2±1.03 years; Table S1). Past population studies shared the similar methodology.[10,14]

The Blood Pressure Category

The entire cohort was categorized by ordinal variables such as normotension (SBP <120 mm Hg and DBP <80 mm Hg, n=1 391 475), prehypertension (120≤ SBP <140 mm Hg and 80≤ DBP <90 mm Hg, n=1 585 311), hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg, n=337 262), and hypertension-medication (no blood pressure criteria, n=766 283). The hypertension group (SBP ≥140 mm Hg or DBP ≥90 mm Hg) included participants who were not taking any antihypertension medication at the time of health screening. For the purpose of our analysis, we defined participants in the hypertension group as having new-onset hypertension. Having at least one hospitalization or 2 outpatient visits with a minimum of one prescription for antihypertension medication with ICD-10 codes I10–I13 or I15 was the criteria for the hypertension-medication group (Table S1).

Variables of Cardiovascular Risk Factors

Smokers were classified as nonsmokers, current smokers, or ex-smokers, and alcohol consumption was categorized into none, mild (≤2 d/wk), or heavy (≥3 d/wk). Regular exercise was defined as vigorous physical activity for at least 20 min/d. Diabetes , dyslipidemia, congestive heart failure, Stroke/transient ischemic accident was confirmed in medical records by corresponding ICD code. The estimated glomerulus filtration rate was derived from the chronic kidney disease epidemiology collaboration equation. A detailed list of the definitions of the variables is provided in Table S1.

Statistical Methods

Categorical variables are presented as frequencies and percentages and were compared using the χ^2 test. Continuous variables are presented as mean and SD or median with range, and they were compared using Student *t* test. For the clinical outcome analysis, incidence rates were estimated using the total number of clinical outcomes during the follow-up period divided by 100 000 person-years at risk. The risk of incident IE according to blood pressure level was analyzed using the Kaplan-Meier method and log-rank test. Cox proportional hazard models were used to analyze the relationship between incident IE and blood pressure in univariable and multivariable analyses. Covariates were incorporated in multivariable analysis for obtaining adjusted hazard ratio and 95% CI, including age, sex, smoke, drink, diabetes, dyslipidemia, congestive heart failure, stroke/transient ischemic accident, IE risk group, body mass index, cholesterol, and glomerular filtration rate.

Cox proportional hazard model was used for subgroup analyses, stratified by age (<65 and ≥65 years), sex, exercise, diabetes, and dyslipidemia. In each subgroup analysis, only the specific subgroups revealing statistically significant (P<0.1) interactions according to blood pressure were evaluated. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC), and all 2-tailed P<0.05 were considered statistically significant.

RESULTS

Study Subjects

The mean age of the cohort was 47.12±14.13 years, with 55.08% males. IE occurred in 812 individuals during the follow-up period. Those who developed IE were more likely to be hypertensive, older, and heavy drinkers and have a history of diabetes, dyslipidemia, stroke or transient ischemic accident, and congestive heart failure (all P<0.001). In the laboratory tests of the health screening exam, those who developed IE had higher levels of lower levels of glomerular filtration rate (P<0.001) and cholesterol (P<0.018). The high-risk group of IE patients with congenital heart disease, implantable cardiac devices, or heart valve prosthesis was associated with a higher risk of developing IE (all P<0.001; Table 1).

Blood Pressure and Incident IE

The incidence rate of IE according to blood pressure was 0.93 person per 100 000 person-years in the normotension group, 1.39 in the prehypertension group, 2.57 in the hypertension group, and 5.96 in the hypertension with medication group. The participants in the prehypertension, hypertension, and hypertension-medication groups all demonstrated higher risks of incident IE in a dose-dependent manner compared with those in the normotension group (hazard ratio [HR], 1.33, [95% CI, 1.06–1.68]; HR, 1.98 [1.48–2.66]; HR, 2.56 [2.02–3.24], respectively; all P<0.001). In the multivariable analysis, higher blood pressure status correlated with increased HR for developing IE in a dose-dependent manner (Table 2, Figure 1). Regardless of IE status, >30% of the participants with hypertension medication had uncontrolled BP (SBP ≥140 or DBP ≥90 mm Hg) and nearly 50% were taking hypertension medication for >5 years (Table S2). The sub-analysis on hypertension-medication group displayed that ACE (angiotensin-converting enzyme) inhibitors/ARB (angiotensin receptor

Table 1. Baseline Characteristics of Participants (n=4 080 331)

Characteristics	Total, N (%)	Infective endocarditis		
		No (%)	Yes (%)	*P* value
N (%)	4080331	4079519 (99.98)	812 (0.02)	
Age				<0.001
20–40	1 284 007 (31.47)	1 283 932 (31.47)	75 (9.24)	
40–60	1 933 610 (47.39)	1 933 342 (47.39)	268 (33)	
60–80	820 883 (20.12)	820 437 (20.11)	446 (54.93)	
80≤	41 831 (1.03)	41808 (1.02)	23 (2.83)	
Sex				0.47
Male	2 247 379 (55.08)	2 246 942 (55.08)	437 (53.82)	
Female	1 832 952 (44.92)	1 832 577 (44.92)	375 (46.18)	
Smoking				0.024
Non	2 420 974 (59.33)	2 420 464 (59.33)	510 (62.81)	
Ex	587675 (14.4)	587 552(14.4)	123 (15.15)	
Current	1 071 682 (26.26)	1 071 503 (26.27)	179 (22.04)	
Alcohol consumption				<0.001
Non	2 101 756 (51.51)	2 101 240 (51.51)	516 (63.55)	
Mild	1 654 077 (40.54)	1 653 849 (40.54)	228 (28.08)	
Heavy	324 498 (7.95)	324 430 (7.95)	68 (8.37)	
Regular exercise	740 160 (18.14)	740 017 (18.14)	143 (17.61)	0.696
Diabetes	359 173 (8.8)	358 991 (8.8)	182 (22.41)	<0.001
Dyslipidemia	742 891 (18.21)	742 681 (18.21)	210 (25.86)	<0.001
Congestive heart failure	23 775 (0.58)	23 722 (0.58)	53 (6.53)	<0.001
Stroke/TIA	67 676 (1.66)	67 635 (1.66)	41 (5.05)	<0.001
Blood pressure level				<0.001
SBP <120 and DBP <80, mm Hg	1 391 475 (34.1)	1 391 355 (34.11)	120 (14.78)	
SBP <140 and DBP <90, mm Hg	1 585 311 (38.85)	1 585 108 (38.86)	203 (25)	
SBP ≥140 or DBP ≥90, mm Hg	337 262 (8.27)	337 183 (8.27)	79 (9.73)	
HP medication	766 283 (18.78)	765 873 (18.77)	410 (50.49)	
IE risk groups				<0.001
Non	407 7947 (99.94)	407 7164 (99.94)	783 (96.43)	
Congenital heart disease	194 (0)	193 (0)	1 (0.12)	
Intracardiac device	1130 (0.03)	1123 (0.03)	7 (0.86)	
Heart valve prosthesis	983 (0.02)	963 (0.02)	20 (2.46)	
Complex	77 (0)	76 (0)	1 (0.12)	
BMI, kg/m^2	23.71±3.45	23.71±3.45	23.89±3.62	0.14
Total cholesterol, mg/dL	195.23±41.6	195.23±41.6	191.78±39.93	0.018
GFR, mL/min/1.73 m^2	87.51±45.06	87.51±45.07	80.95±27.98	<0.001

Complex denotes 2 or more IE high-risk factors present; mean±SD. BMI indicates body mass index; CHF, congestive heart failure; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HP medication, participants taking antihypertensive medications; IE, infective endocarditis; N, number of participants; SBP, systolic blood pressure; and TIA, transient ischemic attack.

blockers) carried 35% higher risk of IE than non-ACE inhibitors/ARB and diuretic revealed 46% increased risk of IE compared with nondiuretic (Table S3).

Subgroup Analyses of Age, Sex, Exercise, Diabetes, and Dyslipidemia

Cox regression analysis was used to evaluate the incidence of IE for specific subgroups, including age, sex, exercise, diabetes, and dyslipidemia (Figure 2). In the explanatory subgroup analysis for incident IE, higher blood pressure (prehypertension, hypertension, hypertension-medication groups) persistently increased the HR of IE in the subgroup of sex and diabetes. However, a significant interaction was observed only in the subgroups of age, regular exercise, and dyslipidemia (Figures 2 and 3).

Of note, the participants who were younger than 65 years, those with no dyslipidemia, and those without regular

Table 2. Incidence Rate and Hazard Ratio for Incident Infective Endocarditis According to Blood Pressure and Other Variables

		Univariable		Multivariable	
Variables	IR*	Hazard ratio (95% CI)	*P* value	Adjusted hazard ratio† (95% CI)	*P* value
Blood pressure level			<0.001		<0.001
SBP <120 and DBP <80, mm Hg	0.930	1 (Ref.)		1 (Ref.)	
SBP <140 and DBP <90, mm Hg	1.386	1.491 (1.19–1.869)		1.385 (1.101–1.742)	
SBP ≥140 or DBP ≥90, mm Hg	2.566	2.764 (2.081–3.672)		2.15 (1.603–2.885)	
HP medication	5.961	6.416 (5.235–7.864)		2.902 (2.294–3.672)	
Age			<0.001		<0.001
20–40	0.628	1 (Ref.)		1 (Ref.)	
40–60	1.495	2.379 (1.842–3.074)		1.962 (1.505–2.558)	
60–80	6.076	9.688 (7.584–12.374)		5.096 (3.858–6.73)	
80≤	7.879	13.027 (8.163–20.79)		5.065 (3.083–8.321)	
Diabetes	5.702	3.113 (2.64–3.672)	<0.001	1.424 (1.145–1.771)	0.002
IE risk group‡	145.717	70.445 (48.626–102.053)	<0.001	21.319 (14.425–31.508)	<0.001
CHF	27.134	13.439 (10.172–17.757)	<0.001	3.766 (2.794–5.078)	<0.001

CHF indicates congestive heart failure; DBP, diastolic blood pressure; HP, antihypertensive medication; IE, infective endocarditis; IR, incidence rate; and SBP, systolic blood pressure.

*IR described per 100 000 person-years.

†Multivariable analysis was adjusted with covariates such as age, sex, smoke, drink, dyslipidemia, stroke/transient ischemic stroke, IE risk group, BMI, cholesterol, and glomerulus filtration rate.

‡IE risk group is defined as those with congenital heart disease, intracardiac device, and heart valve prosthesis.

exercise demonstrated an elevated risk of IE in higher blood pressure groups compared with the normotension control group (Figures 2 and 3). However, only hypertension with medication group displayed an increased risk of incident IE in participants aged >65 years compared with the normotension group (*P* for interaction <0.001). A higher blood pressure level was not a risk factor for incident IE in those who exercised regularly and had dyslipidemia (*P* for interaction = 0.013 and 0.098, respectively). The detailed HRs and 95% CIs are provided in Figure 3.

Hypertension (Hypertension Plus Hypertension With Medication Group) and Incident IE in the High-Risk Group for IE

Among the IE high-risk groups, those with hypertension (hypertension group plus hypertension with medication group) displayed a tremendous increase in the HR of incident IE when compared with the normotension group without IE high-risk factors (HR, 39.53 [25.32–61.72]; Table 3). Among the participants without high-risk factors of IE, hypertension doubled the risk of IE when compared with the normotension group (HR, 2.00 [1.69–2.36], Table 3). Hypertension in the high-risk group displayed statistically significant increase in the risk of IE compared with normotension in the high-risk group (HR, 3.20 [1.149–8.888]; *P* value, 0.026; Table S4).

DISCUSSION

This is the first nationwide, population-based study to analyze the association between high blood pressure and incident IE. Prehypertension, new-onset hypertension, and hypertension with medication groups all demonstrated increased incidence and risk of IE in a dose-response manner. A high-risk patient with IE with hypertension or with antihypertensive medication was associated with a 40× higher risk of developing IE compared with those with normotension without high-risk factors for IE. In subgroup analysis, those without cardiovascular risk factors (eg, age <65, no dyslipidemia, or no regular exercise) were affected by high blood pressure in incident IE.

Notable findings include the increased risks of IE in the participants treated with hypertension medication and also in those with hypertension in high-risk group for IE. There was a possibility that some of the pharmacological agents used for therapy might have contributed to the development of IE. Among the hypertension medications, ACE inhibitor/ARB were correlated with higher incidence of IE than no ACE inhibitor/ARB and diuretic use was associated with increased risk of IE when compared with no diuretic use. We do not report a causal relationship but rather we postulate that the participants with hypertension with medication were at increased risk for cardiovascular diseases, including IE. The potential reasons include the fact that >30% of these patients have uncontrolled BP (SBP ≥140 or DBP ≥90) and about 50% of these patients have been on hypertension medication for >5 years before the health check-up in 2009 (Table S2). The participants with hypertension medication were likely at increased susceptibility to valvular pathology due to poor BP control and possible underlying heart diseases. For instance, it is well known

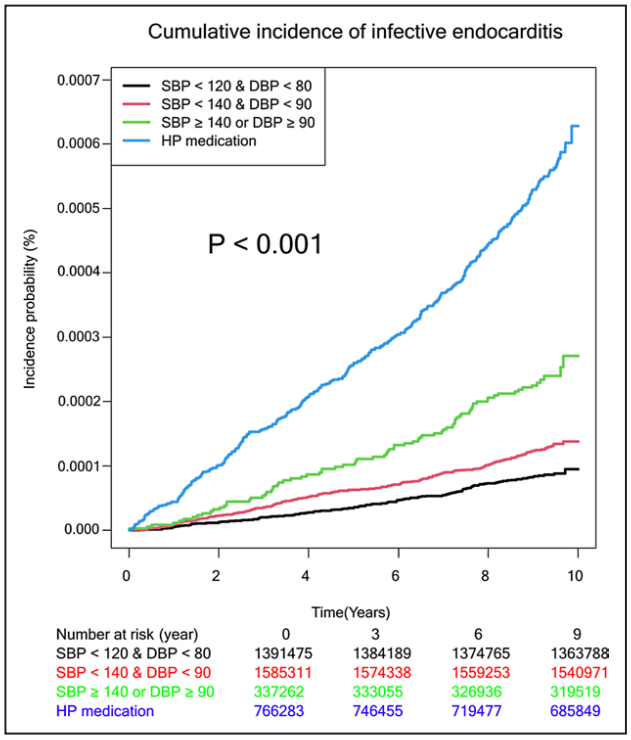

Figure 1. Kaplan-Meier analysis comparing the incidence of infective endocarditis (IE) during the follow-up period in the total cohort.

Higher blood pressure was associated with increased risk of incident IE during the follow-up period. All blood pressure values are in mm Hg. HP medication definition: at least one hospitalization or 2 outpatient visits with a minimum of one prescription for antihypertension medication with *International Classification of Disease, Tenth Revision* codes I10–I13 or I15 (details in Table S1). DBP indicates diastolic blood pressure; and SBP, systolic blood pressure.

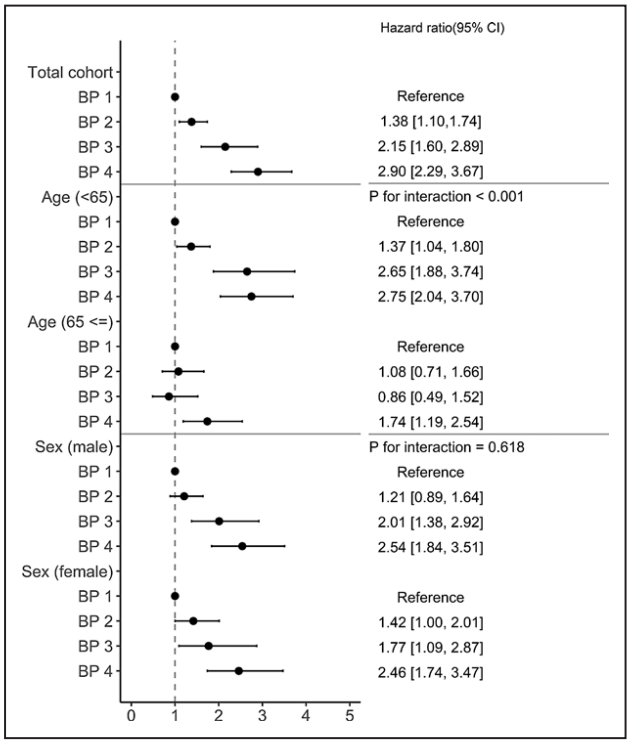

Figure 2. Forest-plot for associated risk of incident infective endocarditis in the subgroup of age and sex according to blood pressure level.

The data are stratified by blood pressure level. BP1 represents systolic blood pressure (SBP) <120 and diastolic blood pressure (DBP) 80, BP2 represents 120≤ SBP <140 and 80≤ DBP <90, BP3 represents SBP ≥140 or DBP ≥90, and BP4 represents those taking antihypertension medication(s). All blood pressure values are in mm Hg.

that the initial treatment for heart failure includes ACE inhibitor/ARB and diuretics and our analysis displayed higher risk for IE in the patients prescribed with ACE inhibitor/ARB than in non-ACE inhibitor/ARB users and higher risk of IE in diuretics than in nondiuretic users. It has been reported that among the hospitalized acute heart failure patients in South Korea from 2004 through 2009, 54% were discharged with ACE inhibitor/ARB.[15] Additionally, hypertensive patients had a greater number of the patients at high-risk for IE than the participants with normal blood pressure (24 versus 5, respectively; Table S4). Such difference likely led to the increased risk of IE in the hypertension group among those at high-risk of IE. Although ACE inhibitor/ARB and diuretics were associated with the increased risk of IE, the drugs are not to be considered harmful given the retrospective study design. However, the possibility of ACE inhibitor/ARB and diuretics increasing the risk of IE cannot be excluded with the current study design.

The association of hypertension to incident IE was not well studied. Previous population studies have discussed hypertension as a risk factor for subsequent major adverse cardiac events following IE rather than a risk factor for IE, and they used only single-center data or dealt with uncommon right-sided IE.[10,11] Moreover, past epidemiological studies have focused on the incidence of IE with respect to the high-risk group of IE or patients with diabetes.[14,16] A recent UK biobank study suggested that blood pressure was associated with incident IE and reduction of blood pressure results in a decrease in the incidence of IE using Mendelian Randomization Study.[9] This study proved that hypertension increases the susceptibility of the heart to infection.

In the literature, the association between high blood pressure and IE occurrence is not clear; however, a few possible suggestions about infection susceptibility arising from high blood pressure are worth mentioning. Hypertension may serve as a major risk factor for valvular heart disease,[17] and valvular heart disease is a known moderate risk factor for incident IE.[7] Mitral regurgitation is the most common valvular heart disease linked with incident IE, and other valvular heart diseases are associated with an increased risk of incident IE.[18] Additionally, hypertension is a risk factor for atherosclerosis and intimal calcification,[19,20] which may, in turn, contribute to infection susceptibility via endothelial injury of the native valves.[21]

ORIGINAL ARTICLE

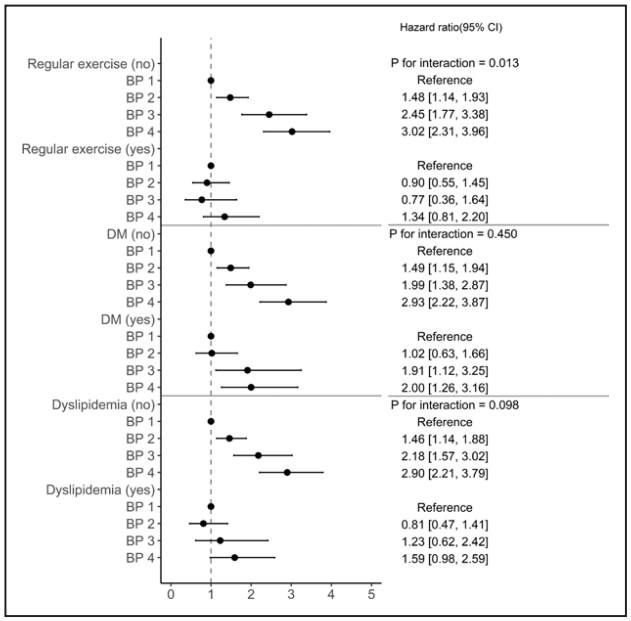

Figure 3. Forest-plot for associated risk of incident infective endocarditis in the subgroups of regular exercise, diabetes (DM), and dyslipidemia according to blood pressure level. The data are stratified by blood pressure level. BP1 represents systolic blood pressure (SBP) <120 and diastolic blood pressure (DBP) <80, BP2 represents 120≤ SBP <140 and 80≤ DBP <90, BP3 represents SBP ≥140 or DBP ≥90, and BP4 represents those taking antihypertension medication(s). All blood pressure values are in mm Hg.

The subgroup analysis revealed that high blood pressure was associated with incident IE in the participants who did not participate in regular exercise. In contrast, no statistically significant association was found between high blood pressure and IE in the participants with regular exercise. Perhaps the lack of exercise played a harmful role in the association between higher blood pressure and IE occurrence and it could be further inferred that regular exercise may help to mitigate the harmful association between high blood pressure and incident IE via exercise-induced paradoxical regression of cardiac remodeling in the hypertensive heart.[22] Likewise, higher blood pressure was associated with increased risk of IE in the participants without dyslipidemia while no meaningful association between high blood pressure and IE was evident in those with dyslipidemia. Perhaps statin played a protective role in the association between high blood pressure and IE.

Thus, we hypothesize that high blood pressure does not directly cause IE and may promote a subclinical state of diseased native valve and formation of atherosclerosis on the endocardium. These processes indirectly promote a condition more prone to acquiring IE. We currently present a retrospective cohort study; therefore, there is a limitation in explaining the causal relationship between hypertension and increased incidence of IE, and this remains to be further explored in future studies.

Limitations

The current study has some limitations. First, it is a retrospective study that carries the risk of inaccuracies in diagnosing the disease of interest. However, previous studies have illustrated that data extraction with ICD codes has reliable validity and predictability in the identification of IE patients.[23,24] Second, although the entire cohort consisted of 4 million participants, the total number of IE cases during follow-up was 812. The incidence rate of IE in the entire cohort was lower than what we had initially anticipated, with an incidence rate of 0.9 in 100 000 for the normotension group and 6.0 in 100 000 in the hypertension-medication group. The low incidence rate limited further statistical analysis, and stringent exclusion criteria were not applicable to retain as many cases of IE as possible. The incidence rate of IE was lower than expected because the current study only sought to analyze the first episode of IE. Furthermore, only the people who were able to willingly participate in the health screening checkups were represented in the NHIS database. Therefore, it is possible that the incidence of IE associated with long-term admissions or long-term care were potentially under-represented with the current research design. Considering the current research methodology, the reported incidence of IE is not an irrational finding. The reported incidences of IE vary depending on different study designs and patient characteristics.[4,14,25] Third, the current cohort consisted of only South Korean participants; therefore, it is difficult to generalize the results

Table 3. Associated Risk of Infective Endocarditis According to Hypertension and IE High-Risk Factors

Hypertension*	IE risk†	Total N	Incident IE	Incidence rate‡	Adjusted HR§	95% CI
No	No	2 975 995	318	1.154	1 (reference)	1 (reference)
	Yes	791	5	73.255	26.904	11.041–65.554
Yes	No	1 101 952	465	4.676	1.997	1.689–2.361
	Yes	1593	24	183.541	39.533	25.323–61.715

IE indicates infective endocarditis; and HR, hazard ratio.

*Hypertension is defined as hospitalization ≥1 or outpatient visit ≥2, with a minimum 1 prescription of an antihypertension drug.

†IE risk group is defined as those with congenital heart disease, intracardiac device, and heart valve prosthesis.

‡Incidence rate is presented as per 100 000 person-years.

§Model adjusted for age, sex, smoking, drinking, regular exercise, diabetes, dyslipidemia, body mass index, chronic heart failure, stroke or transient ischemic attack, total cholesterol, end glomerulus filtration rate, and IE risk.

to other ethnicities. Of note, one of the major risk factors of IE in developed countries is intravenous drug abusers; however, it is worth noting that South Korea has a low incidence of them.[26] Fourth, the reliability of blood pressure measurements during health screening may be challenging. However, a double check-up by an expert medical team was performed during health screening in participants with an abnormal range of blood pressure. Fifth, an unknown amount of residual confounding and bias may be present with a retrospective study design; thus, we excluded missing data and adjusted for possible confounding factors during the analysis. This study does not imply any direct causation between hypertension and IE. However, higher blood pressure was associated with an elevated incidence of IE during the 9-year follow-up in the total cohort. Sixth, it would be clinically meaningful to have hsCRP data available for the analysis but unfortunately, this study did not have access to such data. Lastly, the low number of IE cases in the subgroup analysis weakened the strength of the current study.

Perspectives

The current study demonstrated a dose-dependent relationship between blood pressure and the incidence of IE in a nationwide population database. Therefore, hypertension increases the public health care burden by acting as a risk factor for rare infectious diseases involving the heart.

ARTICLE INFORMATION

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Affiliations

Department of Family Medicine, Korea University Anam Hospital, Korea University, Seoul (G.B.L., K.E.S., Y.-H.K.). Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea (K.H.). Department of Thoracic and Cardiovascular Surgery, Korea University Anam Hospital, Korea University (H.-S.S., J.-S.J., H.-J.K.).

Author Contributions

The corresponding authors declare that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. Study concept and design was performed by H.-J. Kim and Y.-H. Kim. Acquisition of data was performed by K. Han. Analysis and interpretation of data was performed by H.-J. Kim, Y.-H. Kim, G.B. Lee, K.E. Shin, and K. Han. Drafting of the article was performed by G.B. Lee and K.E. Shin. Critical revision of the article was performed by H.-J. Kim, Y.-H. Kim, G.B. Lee, K.E. Shin, H.-S. Son, and J.-S. Jung. Statistical analysis was performed by K. Han.

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