ORIGINAL ARTICLE

# Risk of hypertension on the incidence of out-of-hospital cardiac arrest: A case-control study

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## Abstract

**Objective:** To analyse the effect of hypertension on the occurrence of out-of-hospital cardiac arrest, and to find out whether the effect is dependent on the use of anti-hypertensive drugs.

**Method:** The case-control study used secondary data from the Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance project and comprised patients with presumed cardiac aetiology adult out-of-hospital cardiac arrest assessed by emergency medical service from 27 participating emergency departments from January 2016 to December 2017. Controls matched for age, gender and county were recruited from the Korea National Health and Nutrition Examination Survey database in a 4:1 ratio. Multivariate logistic regression analysis was used to analyse the effects of hypertension and the administration of anti-hypertensive medication on out-of-hospital cardiac arrest incidence. Data was analysed using SAS 9.4.

**Results:** Of the 7330 subjects, 1,466(20%) were patients and 5864(80%) were controls. Hypertension was found in 662(45.2%) patients and 3,190(54.4%) controls. Hypertension lowered the incidence of out-of-hospital cardiac arrest (adjusted odds ratio: 0.69 [95% confidence interval: 0.60-0.80]); in the medication group 0.64(0.55-0.75), and 1.12(0.83–1.49) in the non-medication group.

**Conclusion:** Administration of anti-hypertensive medications in patients of hypertension may help reduce the incidence of out-of-hospital cardiac arrest. Active hypertension diagnosis and anti-hypertensive medications to reduce the incidence of out-of-hospital cardiac arrest is critical.

**Keywords:** Out-of-hospital cardiac arrest, Hypertension, Risk factor. (JPMA 72: 1688; 2022)

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## Introduction

Out-of-hospital cardiac arrest (OHCA) is a major global health problem, with approximately 375,000 OHCA patients being reported in the United States annually.[1] Despite the improvements of resuscitation medicine, the survival rate in OHCA patients over the past decades is very low at 7-8%.[2]

Hypertension (HTN) plays an important role among the established predictors of OHCA.[3] A cohort study involving 1.25 million subjects showed that the lifetime risk of OHCA was about 30% higher in HTN patients than in non-HTN patients and that the risk of sudden cardiac death (SCD) increased by 20% for every 20/10mmHg increase in blood pressure (BP).[4] In addition, HTN is a risk factor for heart failure (HF) and coronary artery disease (CAD) that cause SCD, which, in turn, increases the incidence of cardiac arrest.[5]

HTN is associated with high morbidity and mortality, and generates significant and ongoing financial burden. Previous reports showed that the HTN-related mortality rate in 2015 had increased 1.4-fold compared to 1990.[6] Increase in aging and obese populations are important factors in increasing HTN prevalence. According to the 2018 American Heart Association (AHA) statistics, the incidence of age-adjusted HTN in American adults ages >20 years was 34%, while that in Korean adults aged >30 years was estimated to be 30%.[7]

Large cohort studies have shown a continuous linear association between high BP and cardiovascular disease (CVD) risk[8,9] and meta-analysis of randomised trials demonstrated that the administration of anti-hypertensive medications was associated with a 25% reduction in the initial CVD risk.[10] However, most studies have not focussed on the prevention of OHCA using anti-hypertensive medications. Only one meta-analysis focussing on the incidence of OHCA showed that although the administration of anti-hypertensive medications reduced the incidence of myocardial infarction (MI), it did not reduce OHCA incidence.[11]

Several risk factors for OHCA have been described previously, but their effect on the incidence of OHCA is not completely understood. Therefore, identifying the high-risk population and treatable risk factors is important for preventing the occurrence of OHCA and reducing the burden on public health finances. Although HTN is a well-

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known OHCA risk factor, the variation in the risk of HTN on the incidence of OHCA, depending on the administration of anti-hypertensive medications and age, is unclear.

The current study was planned to analyse the effect of HTN on OHCA incidence, and to find out whether the effect of HTN on the incidence of OHCA depended on the administration of anti-hypertensive medications and age.

## Patients and Methods

The case-control study used secondary data from the Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance (CAPTURES) project[12] and comprised patients with presumed cardiac aetiology adult OHCA assessed by emergency medical service (EMS) from 27 participating emergency departments (EDs0 from January 2016 to December 2017. Controls matched for age, gender and county were recruited from the Korea National Health and Nutrition Examination Survey (KNHANES) database 12) in a 4:1 ratio. The controls were matched for county as it ensured that the controls were representative samples from the same source population. The study protocol was approved by the institutional review boards of the 27 participating institutions, which waived the need for informed consent. The CAPTURES project covers 27 EDs since 2014. The prospective project aims at identifying the risk factors related to OHCA occurrence, and to factors that can predict the prognosis during the follow-up period. This project was targeted at OHCA patients with presumed cardiac aetiology who were transported by EMS with resuscitation and while identifying the ED physicians of each hospital.

The CAPTURES registry carries patient data on demographics, medical history, health behaviour, patient's information of EMS and hospital ED, results of blood test, and clinical outcomes.

Each ED physician interviews the patient or patient's family face-to-face and collect data on a structured survey form. The coordinators collect the findings of cardiac examination and blood test from hospital record reviews, and interview the patient's family members via the telephone for analysis at 6 and 12 months. The project quality management committee (QMC) comprises ED physicians, cardiologists, epidemiologists and statisticians. The QMC gives monthly feedback to coordinators of each hospital through monthly meetings.

KNHANES is a national surveillance monitoring system based on the National Health Promotion Act, and has been carried out every year since 1998 to evaluate the nutritional and health status of Korean nationals. This nationally representative cross-sectional survey is conducted by the Korea Centres for Disease Control and Prevention (KCDC) and collects data on about 0.1 million subjects each year as a study sample. It comprises information on health-related behaviours, socioeconomic status (SES), healthcare utilisation, anthropometric measures, quality of life (QOL), clinical and dietary information collected through health examinations, personal interview and nutrition surveys among the subjects. The health examinations and interviews are conducted by trained personnel, who visit the homes of the enrolled subjects for follow-ups.[13]

The Korean EMS is a government-based, single-tier system. EMS providers can conduct cardiopulmonary resuscitation (CPR) with advanced airway management and autonomic external defibrillation under direct medical control. Termination of resuscitation on scene is not allowed unless there is an obvious mortality sign. The government has categorised EDs into three levels, according to the human resources, instruments, equipment and functional requirements.[14] Detailed information on OHCA protocols, EMS characteristics, and ED characteristics have been reported in literature.[15]

The current study included EMS-assessed adult OHCA patients with a presumed cardiac aetiology who were transferred to the participating hospitals. Paediatric OHCA patients and those with missing data about HTN and medication were excluded.

Critical data element was medical diagnosis of HTN prior to enrollment and treatment; medication or non-medication groups, as measured by the interview survey. Interventions related to exercise and diet were not defined as treatment.

The CAPTURES project and the KNHANES database use the same question items for past medical co-morbidity and health-related behaviours to make the comparison between the patient group and the control group more accurate. The medical history of patients and controls was recorded as "positive" if a condition was clinically diagnosed. Information was collected on age, gender, medical history, including diagnosis of HTN, and health behaviours, such as frequent, occasional or no alcohol intake, smoking, body mass index (BMI) and sleeping hours.

Data was analysed using SAS 9.4. To detect the odds ratio (OR) for exposed subjects relative to unexposed subjects of 1.4, the study needed at least 1450 OHCA patients to be able to reject the null hypothesis using an uncorrected chi-square statistic that the OR equals to 1, with type 1 error of 0.05 and power of 95%.

Chi-square test was used for categorical variables, and Wilcoxon rank sum test for continuous variables. Multiple

imputations with multivariable proportional logistic regression models were conducted for missing variables for health behaviours.

Multivariable logistic regression analysis was performed on the matched case-control dataset to estimate the effect of diagnosis and treatment of HTN on the OHCA risk. Furthermore, the adjusted odds ratios (AORs) and 95% confidence intervals (CIs) were calculated after adjusting for potential confounders. The variables contained in the final model were examined for multi-collinearity between the potential factors.

## Results

Of the 7330 subjects, 1,466(20%) were patients and 5864(80%) were controls (Figure). HTN was found in 662(45.2%) patients. Of them, 566(85.5%) were on anti-hypertensive medications. Among the controls, 3,190(54.4%) had HTN. Among them, 2,950(50.3%) were on anti-hypertensive medications. Previous diagnosis of diabetes was significantly higher in OHCA patients compared to controls ($p$<0.05) (Table 1).

HTN patients on anti-hypertensive medications were more likely to be older and have diabetes and hyperlipidaemia than those not on anti-hypertensive medications ($p$<0.05). Among the HTN patients, the non-medication group was more likely to comprise more current smokers or frequent alcohol consumers than the non-HTN group and the on-medication group (Table 2).

HTN lowered the incidence of OHCA (AOR: 0.69 [95% CI: 0.60-0.80]); in the medication group 0.64(0.55-0.75), and 1.12(0.83–1.49) in the non-medication group (Table 3).

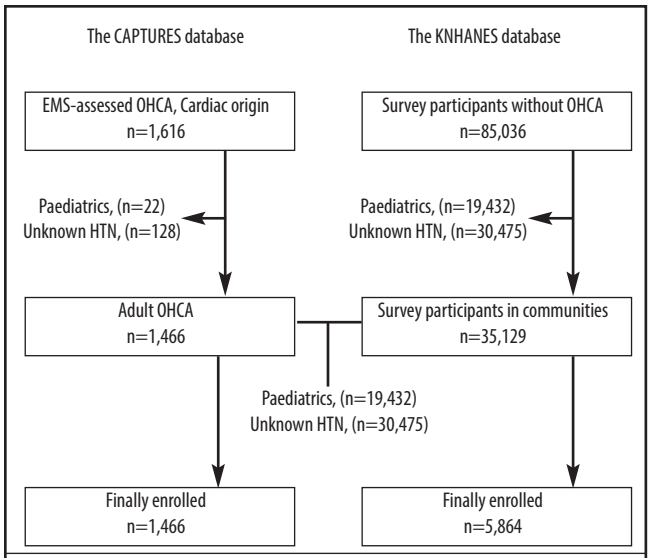


**Figure**: Study population flow. CAPTURES: Cardiac Arrest Pursuit Trial with Unique Registration and Epidemiologic Surveillance; KNHANES: Korea National Health and Nutrition Examination Survey (KNHANES); OHCA, out-of-hospital cardiac arrest; HTN, hypertension.

**Table-1:** Demographics of out-of-hospital cardiac arrest (OHCA) patients and community controls.

| | | Community controls | OHCA cases | |
|---|---|---|---|---|
| | **Total** | **n (%)** | **n (%)** | ***p*-value** |
| **Total** | 7,330 (100.0) | 5,864 (100.0) | 1,466 (100.0) | |
| **Age** (years) | | | | 1.00 |
| 19-29 | 130 (1.8) | 104 (1.8) | 26 (1.8) | |
| 30-39 | 335 (4.6) | 268 (4.6) | 67 (4.6) | |
| 40-49 | 780 (10.6) | 624 (10.6) | 156 (10.6) | |
| 50-59 | 1,415 (19.3) | 1,132 (19.3) | 283 (19.3) | |
| 60-69 | 1,180 (16.1) | 944 (16.1) | 236 (16.1) | |
| 70- | 3,490 (47.6) | 2,792 (47.6) | 698 (47.6) | |
| **Gender** | | | | 1.00 |
| Male | 4,915 (67.1) | 3,932 (67.1) | 983 (67.1) | |
| Female | 2,415 (32.9) | 1,932 (32.9) | 483 (32.9) | |
| **Metropolis** | | | | 1.00 |
| Yes | 4,610 (62.9) | 3,688 (62.9) | 922 (62.9) | |
| **Past medical History** | | | | |
| **Hypertension** | | | | |
| Diagnosis | 3,852 (52.6) | 3,190 (54.4) | 662 (45.2) | <0.01 |
| Treatment | 3,516 (48.0) | 2,950 (50.3) | 566 (38.6) | <0.01 |
| Drug | 3,508 (47.9) | 2,946 (50.2) | 562 (38.3) | <0.01 |
| **Diabetes** | | | | |
| Diagnosis | 1,422 (19.4) | 1,035 (17.7) | 387 (26.4) | <0.01 |
| Treatment | 1,270 (17.3) | 951 (16.2) | 319 (21.8) | <0.01 |
| OHA | 1,119 (15.3) | 860 (14.7) | 259 (17.7) | <0.01 |
| Insulin | 136 (1.9) | 87 (1.5) | 49 (3.3) | <0.01 |
| **Hyperlipidaemia** | | | | |
| Diagnosis | 1,305 (17.8) | 1,221 (20.8) | 84 (5.7) | <0.01 |
| Treatment | 913 (12.5) | 858 (14.6) | 55 (3.8) | <0.01 |
| **Health behaviours** | | | | |
| **Smoking** | | | | <0.01 |
| Current smoker | 1,915 (26.1) | 1,482 (25.3) | 433 (29.5) | |
| Ex-smoker | 2,175 (29.7) | 1,885 (32.1) | 290 (19.8) | |
| Never smoker | 3,240 (44.2) | 2,497 (42.6) | 743 (50.7) | |
| **Alcohol drink** | | | | <0.01 |
| Frequent | 1,850 (25.2) | 1,547 (26.4) | 303 (20.7) | |
| Occasional | 3,786 (51.7) | 3,375 (57.6) | 411 (28.0) | |
| Never | 1,694 (23.1) | 942 (16.1) | 752 (51.3) | |
| **Sleep hour** | | | | <0.01 |
| 0-6 | 1,363 (18.6) | 1,208 (20.6) | 155 (10.6) | |
| 6-8 | 3,636 (49.6) | 3,061 (52.2) | 575 (39.2) | |
| 8-24 | 2,331 (31.8) | 1,595 (27.2) | 736 (50.2) | |
| **BMI** | | | | <0.01 |
| 10.5-18.4 | 310 (4.2) | 165 (2.8) | 145 (9.9) | |
| 18.5-24.9 | 4,400 (60.0) | 3,482 (59.4) | 918 (62.6) | |
| 25.0-50.0 | 2,620 (35.7) | 2,217 (37.8) | 403 (27.5) | |

OHA: Oral hypoglycaemic agent, BMI: Body mass index.

Among those aged >65 years, the incidence of OHCA was lower in HTN patients (AOR: 0.65 [95% CI:0.54–0.78]). However, among participants aged <65 years, there was no significant association between HTN and OHCA (AOR: 1.16 [95% CI: 0.93-1.45]) (Table 4).

**Table-2:** Demographics according to hypertension (HTN) prevalence and treatment.

| | Total | HTN (-) n (%) | HTN and Medication n (%) | HTN and no treatment n (%) | *p*-value |
|---|---|---|---|---|---|
| **Total** | 7,330 (100.0) | 3,478 (100.0) | 3,508 (100.0) | 344 (100.0) | |
| **Case-Control** | | | | | <0.01 |
| Community controls | 5,864 (80.0) | 2,674 (76.9) | 2,946 (84.0) | 244 (70.9) | |
| OHCA cases | 1,466 (20.0) | 804 (23.1) | 562 (16.0) | 100 (29.1) | |
| **Age** (years) | | | | | <0.01 |
| 19-49 | 1,245 (17.0) | 1,033 (29.7) | 146 (4.2) | 66 (19.2) | |
| 50-59 | 1,415 (19.3) | 816 (23.5) | 530 (15.1) | 69 (20.1) | |
| 60-69 | 1,180 (16.1) | 499 (14.3) | 617 (17.6) | 64 (18.6) | |
| 70- | 3,490 (47.6) | 1,130 (32.5) | 2,215 (63.1) | 145 (42.2) | |
| **Gender** | | | | | <0.01 |
| Male | 4,915 (67.1) | 2,467 (70.9) | 2,190 (62.4) | 258 (75.0) | |
| Female | 2,415 (32.9) | 1,011 (29.1) | 1,318 (37.6) | 86 (25.0) | |
| **Metroplolis** | | | | | <0.01 |
| No | 2,720 (37.1) | 1,345 (38.7) | 1,239 (35.3) | 136 (39.5) | |
| Yes | 4,610 (62.9) | 2,133 (61.3) | 2,269 (64.7) | 208 (60.5) | |
| **Diabetes** | | | | | |
| Diagnosis | 1,422 (19.4) | 338 (9.7) | 996 (28.4) | 88 (25.6) | <0.01 |
| Treatment | 1,270 (17.3) | 301 (8.7) | 932 (26.6) | 37 (10.8) | <0.01 |
| OHA | 1,119 (15.3) | 257 (7.4) | 831 (23.7) | 31 (9.0) | <0.01 |
| Insulin | 136 (1.9) | 42 (1.2) | 88 (2.5) | 6 (1.7) | <0.01 |
| **Hyperlipidaemia** | | | | | |
| Diagnosis | 1,305 (17.8) | 332 (9.5) | 915 (26.1) | 58 (16.9) | <0.01 |
| Treatment | 913 (12.5) | 187 (5.4) | 707 (20.2) | 19 (5.5) | <0.01 |
| **Smoking** | | | | | <0.01 |
| Current smoker | 1,915 (26.1) | 981 (28.2) | 815 (23.2) | 119 (34.6) | |
| Ex-smoker | 2,175 (29.7) | 1,010 (29.0) | 1,063 (30.3) | 102 (29.7) | |
| Never smoker | 3,240 (44.2) | 1,487 (42.8) | 1,630 (46.5) | 123 (35.8) | |
| **Alcohol drink** | | | | | <0.01 |
| Frequent | 1,850 (25.2) | 925 (26.6) | 820 (23.4) | 105 (30.5) | |
| Occasional | 3,786 (51.7) | 1,868 (53.7) | 1,766 (50.3) | 152 (44.2) | |
| Never | 1,694 (23.1) | 685 (19.7) | 922 (26.3) | 87 (25.3) | |
| **Sleep hour** | | | | | <0.01 |
| 0-6 | 1,363 (18.6) | 574 (16.5) | 734 (20.9) | 55 (16.0) | |
| 6-8 | 3,636 (49.6) | 1,809 (52.0) | 1,667 (47.5) | 160 (46.5) | |
| 8-24 | 2,331 (31.8) | 1,095 (31.5) | 1,107 (31.6) | 129 (37.5) | |
| **BMI** | | | | | <0.01 |
| 10.5-18.4 | 310 (4.2) | 193 (5.5) | 96 (2.7) | 21 (6.1) | |
| 18.5-24.9 | 4,400 (60.0) | 2,269 (65.2) | 1,926 (54.9) | 205 (59.6) | |
| 25.0-50.0 | 2,620 (35.7) | 1,016 (29.2) | 1,486 (42.4) | 118 (34.3) | |

OHCA: Out-of-hospital cardiac arrest, OHA: Oral hypoglycaemic agent, BMI: Body mass index.

## Discussion

The study observed a lower risk of OHCA among patients diagnosed with HTN. However, in subgroup analysis, the finding was only observed among patients who were administered anti-hypertensive medications, suggesting that the main observed outcome was due to this subgroup of patients.

In the interaction analysis of administration of medications and age, there was no significant relationship between the administration of anti-hypertensive medications and the risk of OHCA in participants aged <65 years, but the risk of OHCA was lower in the medication group among participants aged >65 years. The prevalence of HTN is steadily increasing, and intensive risk management and aggressive treatment need to be emphasised to reduce the burden of HTN and to reduce cardiovascular complications associated with HTN, especially OHCA.

The importance of HTN as a risk factor in SCD is well established.[16] In a study conducted in Finland[17] on a mixed population of patients with and without HTN and CAD, every 10 mmHg increase in systolic and diastolic BP was significantly associated with a 15% and 17% higher risk of SCD, respectively. A recent large cohort study[18] suggested that HTN is an independent risk factor for the incidence of sudden death.

The heart seems to be the most vulnerable organ to HTN, which leads to the development of different degrees of left ventricular hypertrophy (LVH), and there is sufficient evidence indicating that LVH could be responsible for fatal cardiac complications, such as SCD in HTN patients.[19] Many studies have shown that LVH regresses during treatment with anti-hypertensive medications, and preliminary reports have documented that the reduction of LVH leads to a decrease in the risk of SCD.[20-22]

**Table-3:** Multivariable conditional logistic regression analysis of diagnosis and medication for hypertension for out-of-hospital cardiac arrest incidence.

| | OHCA cases/ Community controls n/n | Unadjusted OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|---|
| **Model 1:** HTN diagnosis | | | |
| No | 804/2674 | 1.00 | 1.00 |
| Yes | 662/3190 | 0.69 (0.62-0.77) | 0.69 (0.60-0.80) |
| **Model 2:** HTN treatment | | | |
| Non-HTN | 804/2674 | 1.00 | 1.00 |
| HTN and medication | 562/2946 | 0.64 (0.56-0.72) | 0.64 (0.55-0.75) |
| HTN and no treatment | 100/244 | 1.36 (1.07-1.74) | 1.12 (0.83-1.49) |

OHCA: Out-of-hospital cardiac arrest, OR: Odds ratio, CI: Confidence interval, HTN: Hypertension.

**Table-4:** Multivariable conditional logistic regression analysis for OHCA incidence by age group.

| | Age group | |
|---|---|---|
| | 18 < Age < 65 AOR (95% CI) | Age > 65 AOR (95% CI) |
| **Model 1:** HTN diagnosis | | |
| No | 1.00 | 1.00 |
| Yes | 1.16 (0.93-1.45) | 0.65 (0.54-0.78) |
| **Model 2:** HTN treatment | | |
| No HTN | 1.00 | 1.00 |
| HTN and medication | 1.11 (0.88-1.42) | 0.61 (0.50-0.73) |
| HTN and no treatment | 1.33 (0.89-2.00) | 1.35 (0.91-2.00) |

OHCA: Out-of-hospital cardiac arrest, CI: Confidence interval, HTN: Hypertension, AOR: Adjusted odds ratio.

In contrast to the previous studies,[17,18] the HTN group in the current study did not show a higher incidence of OHCA than that of the general population, highlighting the protective role of anti-hypertensive medications in OHCA.

The risk of cardiac arrest in the medication group was lower than that in the general population, which is inconsistent with the findings of other studies.[23,24] In addition to the results of previous studies[25,26] reporting that anti-hypertensive medication can decrease LVH, the current study postulated two possible reasons.

First, patients diagnosed with HTN and receiving anti-hypertensive medications regularly visited the hospital and were more likely to be diagnosed earlier with other diseases that could cause cardiac arrest, and they would be alerted about their health and perform various health-friendly activities.

Second, some of the patients in the study who were not diagnosed with HTN usually showed a lack of concern for their health and would not test for HTN themselves. It was carefully speculated that these people could have forced overestimation of the risk of OHCA of the normal population.

One of the notable findings of the current study was that anti-hypertensive medications had a significant protective effect against OHCA in patients aged ≥65 years. In the younger age groups, LVH did not progress, and it is likely that the protective effect of anti-hypertensive medications in decreasing the LVH was not significant.[27]

In addition to the increasing temporal trend of HTN prevalence, the population-attributable risk of HTN in cardiac arrest was also substantial. Moreover, the effects of risk factors, such as HTN, on the incidence of cardiac arrest will change with age. In the current study, HTN was not an independent risk factor for OHCA, and the incidence of OHCA in patients who were administered anti-hypertensive medications was lower than that in patients without HTN. This trend was significant at age 65 years or above.

The current study has some limitations. First, the study design was not randomised controlled trial (RCT), and there is a possibility that confounding variables could not have been adjusted. Second, because we measured HTN using a survey questionnaire, the diagnosis of HTN may have been underestimated or overestimated, and some patients with HTN may not have been recorded in the database because they were not diagnosed. Third, the duration of use and type of anti-hypertensive medication was not taken into account. Fourth, the patients were enrolled in 2014, while the controls were enrolled between 2008 and 2017. This difference could be a potential bias factor. Fifth, the researchers at the CAPTURES project were not blinded by research hypothesis that could have led to bias in data collection. Finally, the study could not adjust for unmeasured bias.

## Conclusion

The risk of OHCA was significantly decreased in patients with HTN who were using anti-hypertensive medications than in those not using anti-hypertensive medications as well as in those without HTN.

**Disclaimer:** None.

**Conflict of Interest:** None.

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