The Impact of Abdominal Aortic Aneurysm on Cardiovascular Diseases
A Nationwide Dataset Analysis

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Summary
Cardiovascular diseases (CVDs) including myocardial infarction (MI) and stroke are often diagnosed in patients with abdominal aortic aneurysm (AAA). However, little has been reported regarding the incidence. Patients with AAA were selected from the National Health Insurance system in South Korea between 2009 and 2015. A total of 10,822 participants with a new diagnosis of AAA were included. Propensity score matching by age and sex with patients in whom AAA was not diagnosed was used to select the control group of 32,466 participants. Primary endpoints included the diagnosis of CVD and death. Cox proportional hazard models were used to compare the risk of disease incidence.

The incidence of CVD was 16.573 per 1,000 person-years in the AAA group, which was higher than that of the control group’s 9.30 per 1,000 person-years. The incidence of MI (hazard ratio [HR], 1.7; 95% confidence interval [CI], 1.479-1.953), stroke (HR, 1.629; 95% CI, 1.443-1.839), and CVD (HR, 1.672; 95% CI, 1.522-1.835) was significantly higher in patients with AAA. Mortality rate was also elevated in the AAA group (HR, 2.544; 95% CI, 2.377-2.722).

The incidence of CVD was significantly more frequent in patients with AAA. The AAA group had consistently higher risks regarding CVD and mortality than the control group.

Key words: Myocardial infarction, Stroke, Mortality, Population, Incidence

Cardiovascular diseases (CVDs) rank first in morbidity and mortality worldwide and are the leading cause of death in the United States. CVDs including myocardial infarction (MI) and stroke are often diagnosed in patients with abdominal aortic aneurysm (AAA). However, little has been reported regarding the incidence of CVD in patients with AAA.

Although the initiation and progression pathogenesis of AAA is still poorly understood, AAA and atherosclerosis share multiple mechanisms and risk factors in development. With a higher risk of developing MI or stroke, patients with AAA would need preventive action against developing CVD.

In Western countries, AAA is regarded as a common and preventable cause of cardiovascular death. The number of AAAs in South Korea also increased in recent years. The aim of this retrospective study using a large dataset was to demonstrate the incidence of CVD in AAA compared with the control group.

Method
The Korean National Health Insurance (NHI) system and Medical Aid (MA) are two major health care programs for general coverage of all people in South Korea. The NHI system guarantees almost 97% of people, and MA secures approximately 3% of residents. The NHI system provides all insured Koreans biannual health examinations. Therefore, the NHI system can gain extensive data from Korean residents including patient demographics, medical treatment and procedures, and disease diagnoses according to the International Classification of Disease, 10th edition. For this study, data from 2009 to 2015 were collected from the NHI system database.
The AAA group was defined as patients who were diagnosed with AAA codes I713, I714, I715, I716, I718, or I719 more than twice at outpatient departments in a year or had been hospitalized for AAA codes more than once or had open surgical aneurysm repair (OSAR) or endovascular aneurysm repair (EVAR) surgery between January 2009 and December 2015. MI codes were defined as I210-I219, and stroke codes were defined as I63 and I64. CVDs are a wide range of diseases, but in this study, CVD included only MI and stroke.

Primary endpoints included CVD diagnosis and death. We excluded patients who had not had a health examination within 2 years prior to the diagnosis of AAA (n = 26,121), were younger than 20 years old (n = 2), had a previous diagnosis of MI (n = 2,755), had a previous diagnosis of stroke (n = 4,503), or had data missing (n = 162). Patients who were diagnosed with MI or stroke within 1 year from diagnosis of and surgery for AAA were also excluded. The control group was composed of triple the number of age- and sex-matched test group participants (Figure 1).

The demographic variables included age (< 65 versus ≥ 65 years); sex; income level (receiving MA and income within the lowest 20%); presence of diabetes mellitus (E11-14 or fasting glucose level ≥ 126), hypertension (I10-13 and I15 with anti-hypertensive medication or systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90), or dyslipidemia (E78 with anti-hyperlipidemic medications or total cholesterol ≥ 240); performance of regular exercise (mid-term exercise ≥ 5 days or vigorous exercise ≥ 3 days in a week); and presence of chronic kidney disease (estimated glomerular filtration rate < 60 mL/minute/1.73 m²). Tobacco use and alcohol consumption were subdivided in accordance with current smoker or heavy drinker. Abdominal obesity (waist circumference ≥ 90 in men and ≥ 85 in women) and body mass index (BMI) (< 25 versus ≥ 25 kg/m²) were also included in subgroup analysis.

The statistical analyses were conducted using SAS Enterprise Guide 6.1 and SAS Enterprise Miner 13.2 (SAS Institute Inc., Cary, NC, USA). This study was conducted with approval from the Institutional Review Board of the Catholic University of Korea, Eunpyeong St. Mary’s Hospital, Seoul, Korea (PC20ZISI0146). The data were provided in the remote analysis system from the NHI system. Continuous variables are presented as mean ± standard deviation, and categorical variables are presented as number (percentage). To compare characteristics between the patient and control groups, the Student’s t-test was used for continuous variables, and the chi-square test or Fisher’s exact test for categorical variables. The incidence rates of CVD (MI and stroke) are presented as per 1,000 person-years. Multivariate Cox regression models were used to evaluate the association between the absence or presence of AAA and the incidence of new-onset CVD. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the outcome were calculated in the AAA group and control group. There were no adjusted data of hazard in Model 1. The Cox proportional regression models were adjusted for the demographic variables (age; sex; income; and presence of hypertension, diabetes mellitus, and dyslipidemia) in Model 2 and further adjusted for all covariates (age; sex; tobacco use; alcohol consumption; performance of regular exercise; BMI; income level; and presence of diabetes mellitus, hypertension, and dyslipidemia) in Model 3.

Results

A total of 10,822 patients were enrolled in this study among 45,767 patients who had treatment codes for AAA between January 2009 and December 2015. The control group was composed of 32,466 age- and sex-matched subjects. Table I shows the demographic data. Current smokers were more frequent in the AAA group (27.13% versus 18.74%, P < 0.001). Heavy alcohol consumers were more frequent in the AAA group (7.24% versus 6.84%, P < 0.001). Patients in the AAA group exercised less regularly (20.75% versus 22.81%, P < 0.001). The AAA group had a higher morbid rate for diabetes mellitus, hypertension, and dyslipidemia. In height and weight, patients in the AAA group were taller and heavier (P < 0.001). BMI and waist circumference were higher in the AAA group (P < 0.001). Glomerular filtration rate was lower in the AAA group (P < 0.001).

The incidence of CVD was 16.573 per 1,000 person-years in the AAA group, which was higher than that of the control group’s 9.30 per 1,000 person-years. Table II presents the HR for MI, stroke, CVD, and death in the AAA group. The incidence of MI (HR, 1.7; 95% CI, 1.479-1.953), stroke (HR, 1.629; 95% CI, 1.443-1.839), and CVD (HR, 1.672; 95% CI, 1.522-1.835) was significantly higher in patients with AAA. The cause of mortality was not confined specifically to MI or stroke. Overall, mortality rate was higher in the AAA group (HR, 2.544; 95% CI, 2.377-2.722).

Figure 2 shows the Kaplan-Meier curves for the incidence probability of MI, stroke, CVD, and death. The AAA group had significantly higher probability in all categories than the control group (P < 0.0001).

Supplemental Tables I-IV show the subgroup analysis with all variables. In incidence of MI, HRs for waist circumference and BMI were significantly different. Regarding MI, HR of patients with AAA in the no obesity group (waist circumference < 90 in men and < 85 in women) was 1.841 compared with the control group. HR of patients with AAA in the obesity group (waist circumference ≥ 90 in men and ≥ 85 in women) was 1.429 (P for interaction = 0.0368). Although patients with AAA in the BMI < 25 group had a 1.857 HR, the HR in the BMI ≥ 25 group was 1.438 (P for interaction = 0.0245). Risk of MI in the AAA group was more prominent in less obese patients (smaller waist circumference and lower BMI).

In stroke hazard analysis, older age was the significant variable. Patients with AAA aged < 65 years had a 2.104 ratio, but a 1.505 ratio was present for the age ≥ 65 years group (P for interaction = 0.0062). Risk of stroke in the AAA group decreased with advanced age.

CVD hazard analysis showed that patients with AAA < 65 years had a 2.068 HR and ≥ 65 years had a 1.559 HR (P for interaction = 0.004). The HR for CVD was higher in the AAA group for all ages than in the control
Discussion

A prevalence of AAA of 4%-7% has been reported in Western countries, mainly among males older than 65 years. Recent screening showed a decreased prevalence of 1.1%-1.7% in 65-year-old males.8,9 The decline in AAA prevalence was regarded as meaningful after CVD risk management.10 The decline in AAA prevalence was regarded as meaningful after CVD risk management.10

Many investigations regarding the relationship between AAA and atherosclerosis have been reported. Taki-gawa, et al. demonstrated that the concomitant silent athe-
AAA repair, and Jones, CVD was the most important cause of late mortality after Italy. In addition, Goodney, and its relation with CVD risk stratification in Northern population-based study researched the AAA prevalence increased. The RoCA V (Risk of CVD and AAA in Varese) risk of atherosclerotic CVD in patients with AAA was highly increased. The RoCAV (Risk of CVD and AAA in Varese) population-based study researched the AAA prevalence and its relation with CVD risk stratification in Northern Italy. In addition, Goodney, et al. demonstrated that CVD was the most important cause of late mortality after AAA repair, and Jones, et al. investigated the significantly greater prevalence of AAA in individuals with CVD risk.

Hertz was the first to describe the strong relationship between AAA and coronary artery disease in 1984. Since, many data have shown that patients with AAA had increased risk of atherosclerotic thrombosis such as MI and stroke. Multifactorial and polygenic factors such as genetics, lifestyle, and environmental risk factors synergistically affect the development and progression of AAA. The association between AAA and atherosclerosis is not yet fully understood; whether the relationship is

### Table I. Characteristics of Subjects

| Variables                  | AAA | P-value |
|----------------------------|-----|---------|
| n                          | 32,466 | 10,822 |
| Age                        | 63.88 ± 11.74 | 63.88 ± 11.74 | 1 |
| Sex, male                  | 20,775 (63.99) | 6,925 (63.99) | 1 |
| Smoking status             | < 0.0001 |
| Non                       | 18,996 (58.51) | 5,476 (50.6) |
| Ex                        | 7,386 (22.75) | 2,410 (22.27) |
| Current                    | 6,084 (18.74) | 2,936 (27.13) |
| Alcohol consumption         | < 0.0001 |
| Non                       | 19,555 (60.23) | 6,929 (64.03) |
| Mild                      | 10,690 (32.93) | 3,109 (63.99) | 1 |
| Heavy                     | 2,221 (6.68) | 784 (7.24) |
| Regular exercise           | < 0.0001 |
| 7,405 (22.81)             | 2,246 (20.75) |
| Diabetes mellitus          | 0.0182 |
| 5,537 (17.05)             | 1,953 (18.05) |
| Hypertension               | < 0.0001 |
| 15,590 (48.02)            | 7,984 (73.78) |
| Dyslipidemia               | < 0.0001 |
| 9,517 (29.31)             | 5,492 (50.75) |
| Income level, low          | 0.6694 |
| 6,090 (18.76)             | 2,010 (18.57) |
| Weight (kg)                | < 0.0001 |
| 62.84 ± 10.62              | 63.8 ± 11.32 |
| Height (cm)                | < 0.0001 |
| 161.87 ± 8.84             | 162.83 ± 9.2 |
| BMI (kg/m²)                | 0.0399 |
| 23.91 ± 3.07              | 23.98 ± 3.2 |
| Waist circumference (cm)   | < 0.0001 |
| 82.79 ± 9.92              | 83.67 ± 8.88 |
| SBP (mmHg)                 | < 0.0001 |
| 126.72 ± 15.33            | 127.89 ± 16.57 |
| DBP (mmHg)                 | < 0.0001 |
| 77.29 ± 9.88              | 78.25 ± 10.85 |
| Glucose (mg/dL)            | < 0.0001 |
| 102.85 ± 25.66            | 101.13 ± 23.94 |
| Cholesterol               | 0.4659 |
| 194.88 ± 43.66            | 195.23 ± 43.2 |
| HDL (mg/dL)                | < 0.0001 |
| 53.52 ± 17.19             | 51.88 ± 23.06 |
| LDL (mg/dL)                | 0.0055 |
| 115.56 ± 62.02            | 117.38 ± 49.37 |
| GFR (mL/minute/1.73 m²)    | < 0.0001 |
| 80.7 ± 38.5               | 77 ± 33.44 |

AAA indicates abdominal aortic aneurysm; BMI, body mass index; DBP, diastolic blood pressure; GFR, glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; and SBP, systolic blood pressure.

### Table II. Hazard Ratios for MI, Stroke, CVD, and Death in the AAA Group

| Event | AAA | n   | Duration | IR_PHER1000 | Model 1 HR (95% CI) | Model 2 HR (95% CI) | Model 3 HR (95% CI) |
|-------|-----|-----|----------|-------------|---------------------|---------------------|---------------------|
| All   | No  | 32,466 | 10,822 |
|      |     |       |          |             |                     |                     |                     |
| MI    | No  | 620  | 153,195.45 | 4.04712 | 1 (Ref.)            | 1 (Ref.)            | 1 (Ref.)            |
|      | Yes | 350  | 46,303.18  | 7.55887  | 1.887 (1.655–2.152) | 1.815 (1.583–2.081) | 1.7 (1.479–1.953)  |
| Stroke| No  | 855  | 152,588    | 5.6033   | 1 (Ref.)            | 1 (Ref.)            | 1 (Ref.)            |
|      | Yes | 443  | 46,046.7   | 9.62067  | 1.726 (1.538–1.935) | 1.7 (1.508–1.915)  | 1.629 (1.443–1.839) |
| CVD   | No  | 1,409 | 151,495.57 | 9.3006   | 1 (Ref.)            | 1 (Ref.)            | 1 (Ref.)            |
|      | Yes | 754  | 45,494.73  | 16.5733  | 1.795 (1.643–1.962) | 1.76 (1.605–1.93)  | 1.672 (1.522–1.835) |
| Death | No  | 2,181 | 154,401.6  | 14.1255  | 1 (Ref.)            | 1 (Ref.)            | 1 (Ref.)            |
|      | Yes | 1,677 | 46,892.3   | 35.7628  | 2.553 (2.396–2.721) | 2.772 (2.593–2.963) | 2.544 (2.377–2.722) |

AAA indicates abdominal aortic aneurysm; HR, hazard ratio; CI, confidence interval; CVD, cardiovascular disease; IR_PHER1000, incidence rates per 1,000 person-years; and MI, myocardial infarction. Model 1: no adjusted data of hazard. Model 2: adjusted for the demographic variables (age, sex, income, hypertension, diabetes mellitus, and dyslipidemia). Model 3: adjusted for all covariates (age, sex, smoking, drinking, regular exercise, BMI, income level, diabetes mellitus, hypertension, and dyslipidemia).
causal or the result of shared risk factors has not been determined. One theory suggests that processes from aortic atherosclerosis promote AAA development. Another theory advocates that genetic and environmental factors directly stimulate AAA formation. There are some similarities and differences in risk factors between atherosclerosis and AAA. Similarities include tobacco use, presence of hypertension, and obesity. However, presence of diabetes is a negative or neutral risk factor for AAA. Our investigation presented some characteristics of those diagnosed with AAA (Table I). This group smoked more and had more obesity. Hypertension, diabetes, and dyslipidemia were more frequent in the AAA group. Patients with AAA also had lower high-density lipoprotein levels and higher low-density lipoprotein (LDL) levels. These features could be related to the development of atherosclerosis and CVD.

Here, with epidemiologic data, we analyzed the incidence of CVD in patients with AAA in South Korea. Patients who were not detected with CVD until 1 year after diagnosis of AAA were enrolled in our study. HRs for MI, stroke, CVD, and mortality in the AAA group were higher, respectively, than those in the control group. Additionally, there were some factors that had significant differences in subgroups such as obesity, BMI, older age, and presence of diabetes and hypertension. Our conclusion is that the AAA group obviously had consistently higher risks regarding CVD and mortality than the control group.

The 2019 American College of Cardiology/American Heart Association guidelines on primary prevention of CVD insist that most atherosclerotic CVD is avoidable through primary prevention and control of risk factors. The primary prevention of CVD consisted of healthy diet, regular exercise, glycemic control, and weight control. When 10-year CVD risk is ≥20%, the guidelines recommended the use of a high-intensity statin to reduce LDL

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Figure 2. Kaplan–Meier curve. Log-rank $P$-value < 0.001. AAA indicates abdominal aortic aneurysm; CVD, cardiovascular diseases; and MI, myocardial infarction.
chol est er to $\geq 50\%$. When 10-year CVD risk is $\geq 10\%$
and a systolic blood pressure of 130 mmHg or higher or a
diastolic blood pressure of 80 mmHg is present, the use
of blood pressure lowering medications was recom-
mended. For those who are at higher CVD risk, but not at
increased risk of bleeding, low-dose aspirin (75-100 mg
orally daily) can also be considered, and the requirement
for smoking cessation is absolute.\textsuperscript{11}

Currently, the most common treatment for AAA is
OSAR or EVAR. In asymptomatic AAA, main manage-
ment is composed of risk reduction and surveillance.\textsuperscript{20}
Ul-trasonographic surveillance is recommended at each time
interval, and the time interval is determined by AAA size.
Smoking cessation and blood pressure control are benefi-
cial for control of small AAAs. Based on AAA pathology
theory, ongoing trials to examine stem cell therapy and
use of cyclosporin A, doxycycline, ticagrelor, and
angiotensin-receptor blocker are being conducted.\textsuperscript{21}

No treatment to prevent the expansion and rupture of
AAA is currently available. However, there were many
lifestyle modifications and some drugs to prevent athero-
sclerotic CVD. In this report, the incidence of CVD was
significantly more frequent in patients diagnosed with
AAA. Primary prevention of CVD in patients diagnosed
with AAA should be considered proactively.

Due to the limitations of NHI data, the impact of pri-
mary prevention of CVD in patients with AAA could not
be determined. Further studies are needed to determine
the value of statin, aspirin, and glycemic and blood pres-
sure control medications for primary prevention of CVD
in patients with AAA. CVD was defined as only MI and
stroke in our study, although CVD encompasses a wider
spectrum of disease. Therefore, the incidence of CVD in
AAA might be underestimated in this article.

In conclusion, the incidence of CVD was signifi-
cantly more frequent in the AAA group than in the con-
tral group. Because the risk for CVD and mortality was
consistently higher in patients with AAA, it is considered
that patients diagnosed with AAA may need efforts to
prevent CVD. Thus, further research is needed to evaluate
how effective the primary prevention of CVD will be in
the AAA population.

Disclosure

Conflicts of interest: None.

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Supplemental Files

Supplemental Tables I-IV
Please see supplemental files at https://doi.org/10.1536/ihj.21-328.