Original Article
Yonsei Med J 2022 Dec;63(12):1069-1077
https://doi.org/10.3349/ymj.2022.0111

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Major Adverse Cardiovascular Events in Korean Congenital Heart Disease Patients: A Nationwide Age- and Sex-Matched Case-Control Study

Jue Seong Lee[1]*, Jin-Man Jung[2,3]*, Jongun Choi[4], Woo-Keun Seo[4], and Hong Ju Shin[5]

[1]Department of Pediatrics, Korea University Anam Hospital, Korea University College of Medicine, Seoul;
[2]Department of Neurology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan;
[3]Korea University Zebrafish Translational Medical Research Center, Ansan;
[4]Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul;
[5]Department of Thoracic and Cardiovascular Surgery, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea.

Purpose: Congenital heart disease (CHD) is a known risk factor for acquired cardiovascular and cerebrovascular diseases. However, available evidence on CHD is limited mostly to Western populations. This study aimed to evaluate the prevalence of vascular events and all-cause mortality in Korean patients with CHD and to further corroborate CHD as a predictor of vascular events and all-cause mortality.

Materials and Methods: The claims data of the Korean National Health Insurance Service (NHIS) were retrospectively reviewed. Information regarding diagnostic codes, comorbidities, medical services, income level, and residential area was also collected. Outcomes of interest included stroke, myocardial infarction (MI), all-cause mortality, and major adverse cardiovascular events (MACE).

Results: We included 232203 patients with CHD and 3024633 individuals without CHD as a control group through age- and sex-matched 1:10 random sampling. The prevalences of hypertension, congestive heart failure, ischemic heart disease, hyperlipidemia, and atrial fibrillation were significantly higher in the CHD group, which had a more than two-fold higher incidence of vascular events and all-cause mortality, than in the group without CHD. Multivariable models demonstrated that CHD was a significant risk factor for stroke, MI, all-cause mortality, and MACE.

Conclusion: In conclusion, this nationwide study demonstrates that Korean patients with CHD have a high incidence of comorbidities, vascular events, and mortality. CHD has been established as an important predictor of cardiovascular events. Further studies are warranted to identify high-risk patients with CHD and related factors to prevent vascular events.

Key Words: Congenital heart disease, vascular events, all-cause mortality, Korean nationwide study

Received: April 22, 2022 **Revised:** September 30, 2022 **Accepted:** October 11, 2022 **Published online:** November 9, 2022
Co-corresponding authors: Woo-Keun Seo, MD, PhD, Department of Neurology and Stroke Center, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea.
E-mail: mcastenosis@gmail.com and
Hong Ju Shin, MD, PhD, Department of Thoracic and Cardiovascular Surgery, Korea University Ansan Hospital, Korea University College of Medicine, 123 Jeokgeum-ro, Danwon-gu, Ansan 15355, Korea.
E-mail: babymedi@naver.com

*Jue Seong Lee and Jin-Man Jung contributed equally to this work.
•The authors have no potential conflicts of interest to disclose.

INTRODUCTION

Congenital heart disease (CHD) is the most common congenital anomaly, affecting 1% of births.[1,2] Although the prevalence of severe CHD is decreasing, the overall prevalence of CHD is reportedly increasing worldwide due to advances in medical care.[2,3] Moreover, the survival rate of patients with CHD has improved dramatically, and currently, more than 90% of patients can survive to adulthood. Hence, the adult congenital heart disease (ACHD) population is increasing.[4,5] However, the health system resources for CHD, including per capita income, education level, childbirth rate, pediatric cardiologists, and cardiovascular centers, differ between countries and could contribute to different outcomes.[6,7] For several decades, the Republic of Korea has undergone marked economic development and progress. Improvements in the healthcare sector have resulted in an increased prevalence of patients with ACHD, as the long-term prognosis of infants and children with CHD has improved.[8,9] Korea has a well-developed health insurance system; hence, almost all patients can receive health insurance benefits. Nevertheless, the possibility that vascular events occur more frequently at lower income levels suggests that patients in these population groups may have poorer health behaviors, including unhealthy dietary habits, lack of exercise, excessive drinking, or smoking. Thus, the outcomes may differ.[10,11]

In Western literature, CHD has attracted considerable attention as a risk factor for cardiovascular events. As the survival rate of CHD patients has improved, cardiovascular diseases, such as atrial fibrillation (AF), heart failure, and ischemic heart disease (IHD), are frequently seen in these patients. Researchers have also noted an earlier onset and higher prevalence of acquired cardiovascular diseases, including IHD and stroke, in CHD patients.[5,12,13] However, such evidence based on nationwide or population-based studies cannot be extrapolated because they are mainly limited to Western populations rather than the Korean population. Epidemiological information, including long-term prognosis, using nationwide data from Korean patients with CHD is required.

The purpose of this study was to evaluate the prevalence of vascular events and all-cause mortality in Korean CHD patients using nationwide data and to further confirm CHD as an important predictor of vascular events and all-cause mortality in CHD patients.

MATERIALS AND METHODS

Data source

The Korean National Health Insurance Service (NHIS) claims data were retrospectively reviewed. The Korean NHIS covers all citizens of the Republic of Korea and has a registered population of approximately 50 million.[14] The Korean NHIS data encompass diagnostic codes according to the International Classification of Disease, Tenth Revision (ICD-10), as well as demographic characteristics, including sex, age, economic status, residential area, and medical information, such as prescriptions, tests, procedures, and any procedures performed during inpatient visits and hospitalizations.

Study population

Based on the entire dataset from the NHIS from January 1, 2006 to December 31, 2017, a group of patients who received a first diagnosis code related to CHD was initially extracted (Fig. 1). This included patients diagnosed with CHD before 2006, as well as CHD for the first time since 2006 and being followed up. The follow-up duration for these patients was from the date first allocated to the diagnosis of CHD (index date) to the date when the outcomes were ascertained or censored. The ICD-10 codes assigned to the CHD group are presented in Supplementary Table 1 (only online). The control group was selected after age- and sex-matched random sampling at a 1:10 ratio (case vs. control) from the entire dataset of participants without CHD, as described in previous studies.[15,16]

Definition and classification of associated factors

We documented history of hypertension (HTN), diabetes mellitus (DM), IHD, and stable and unstable angina including myocardial infarction (MI), regardless of stent insertion or coronary artery bypass graft (CABG), congestive heart failure (CHF), hyperlipidemia, and AF. In cases of HTN and DM, if there was a history of prescribing related drugs and the related diagnostic codes were repeated at least twice, the patient was considered to have the corresponding disease. Other comorbidities were assigned to patients if the associated diagnostic code was repeated at least twice. Cardiovascular procedures, including percutaneous coronary intervention (PCI), CABG, defibrillator, pacemaker, and valve replacement, were considered to have been performed if there was an associated procedure or operation code. Moreover, economic status was divided into four levels according to income bracket: The fourth income quartile implies the lowest level and the first income quartile implies the highest level. To classify residential areas, the entire Republic of Korea was divided into six regions based on administrative districts: metropolitan areas including Seoul/Gyeonggi-do/Incheon, Gangwon-do, Chungcheong-do, Gyeongsang-do, Jeolla-do, and Jeju-do.

Characteristics of CHD

We classified CHD into severe, shunt, right-sided, left-sided, and other lesions, and cyanotic CHDs by referring to a previous report (Supplementary Table 2, only online).[17] Each CHD category could overlap. Tetralogy of Fallot, endocardial cushion defects, single ventricle, transposition complex, and truncus arteriosus were classified as severe lesions. Atrial septal, ventricular septal, patent ductus arteriosus, and atrioventricular septal defects were classified as shunt lesions. Congenital

https://doi.org/10.3349/ymj.2022.0111

mitral steno-insufficiency, congenital aortic steno-insufficiency, and aortic coarctation were classified as left-sided lesions. Ebstein anomaly, congenital tricuspid valve disease, pulmonary artery anomalies, and pulmonary valve anomalies were classified as right-sided lesions. Anomalies of the great veins and no single leading CHD lesion were classified as other lesions. Tetralogy of Fallot, truncus arteriosus, double-outlet right ventricle, transposition complex, single ventricle, tricuspid atresia, hypoplastic left heart syndrome, and total anomalous pulmonary venous connections were classified as cyanotic lesions.

Outcomes of interest

The outcomes of interest were any stroke, MI, all-cause mortality, and major adverse cardiovascular events (MACE). Stroke was defined as the occurrence of a cerebral image taken at the time of hospitalization, with a related diagnostic code (I60–I63). MI was defined as the occurrence of an event if hospitalization occurred according to the corresponding diagnostic code (I21). All-cause mortality was defined as the death of a patient irrespective of the cause of death. Information about death was linked to the Korean NHIS data, without the cause of death. Finally, MACE included vascular events, such as angina (I20), acute MI (I21), cardiovascular disease (I00–I99) requiring coronary revascularization procedures (PCI or CABG), atherosclerotic heart disease (I25.1), any stroke (I60–I63), peripheral vascular disease (I73) requiring hospitalization, and all-cause mortality.

This study was approved by the Institutional Review Board of the Korea University Ansan Hospital (AS0162) and the need for informed consent was waived because of the retrospective study design. All participant identification numbers in the database were de-identified and encrypted to protect their privacy; thus, the submission of informed consent was exempted.

Statistical analysis

Continuous variables are expressed as means±standard deviations (SD) or medians (interquartile range, IQR), as appropriate, and categorical variables are expressed as numbers and percentages. Continuous variables were compared using Student's t-test or the Wilcoxon signed-rank test depending on the

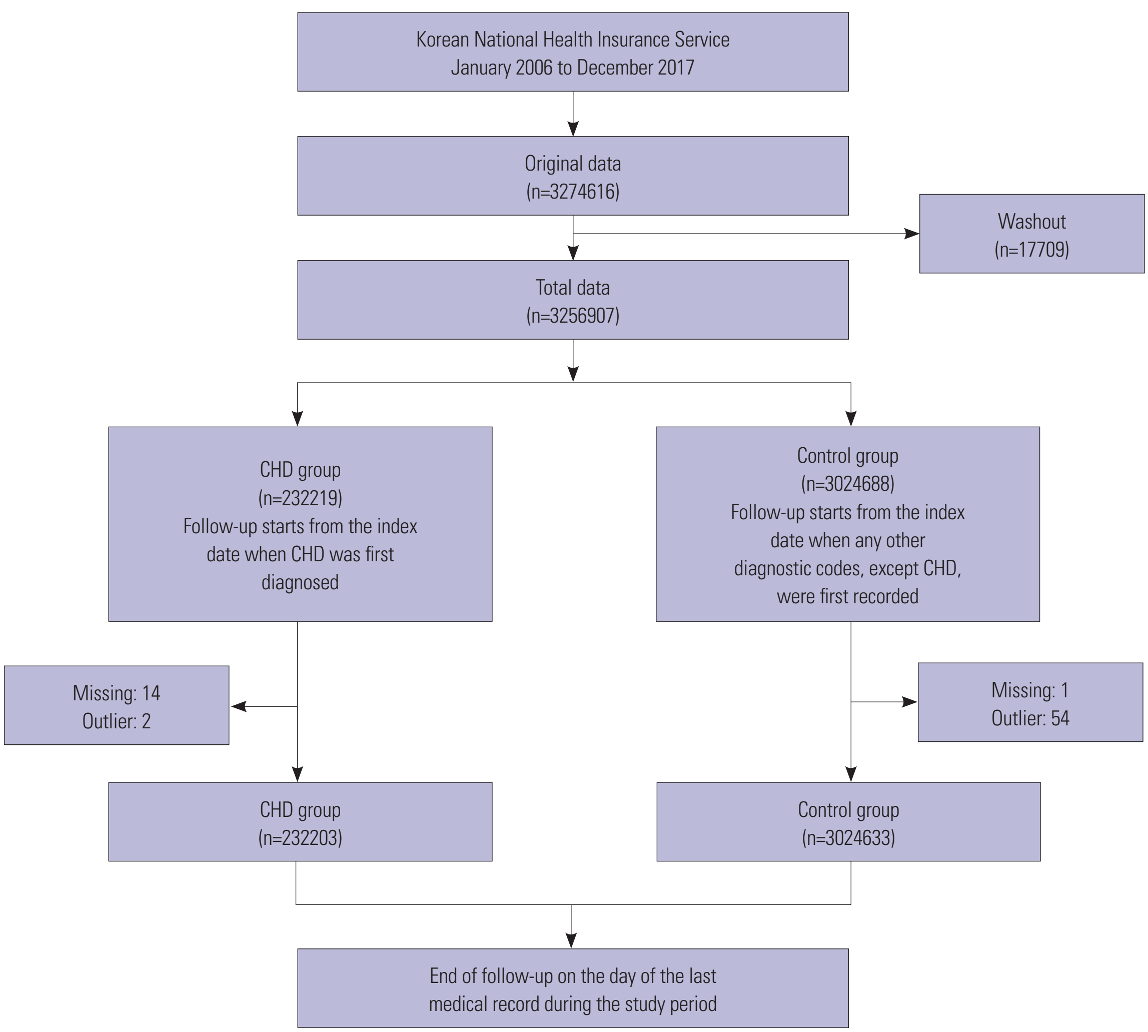

Fig. 1. Flowchart of the study population. CHD, congenital heart disease.

normal distribution of variables, and categorical variables were compared using the chi-square test. The incidence rate of the outcomes was calculated as the ratio of each event to the total person years. The cumulative event rates for each outcome were compared between the two groups using the log-rank test. For subgroup analyses, we performed analyses restricted to patients aged >20 years to evaluate the relationship between ACHD and vascular events. To investigate whether CHD can be a risk factor for vascular events and all-cause mortality, a Cox proportional hazards model was used for MACE and all-cause mortality, and a competing risk analysis was adopted for stroke and MI, in which mortality could be a competing event. Variables with $p<0.05$ in univariable analyses were entered into the multivariable analyses. Statistical significance was set at $p<0.05$. Statistical analyses were performed using SAS software version 7.1 (SAS Institute, Cary, NC, USA).

RESULTS

In this study, 3256907 participants were screened. Patients diagnosed with stroke before the allocation of CHD diagnosis codes were excluded from the washout period. We included 232203 patients in the CHD group and 3024633 patients without CHD in the control group (Fig. 1). The median follow-up period was 7.28 (IQR 3.59–8.73) years.

Baseline characteristics

The baseline patient characteristics are presented in Table 1. The mean age of the CHD group was 12.8±19.9 years, and that of the control group was 13.2±19.8 years. The prevalences of HTN, IHD, CHF, hyperlipidemia, and AF were significantly higher in the CHD group than in the control group. All cardiac procedures or surgeries, including PCIs, CABGs, defibrillators, pacemakers, and cardiac valve replacements, were performed more frequently in the CHD group. Furthermore, antithrombotic agents and statins were prescribed more frequently in the CHD group than in the control group. There was a significant difference between the two groups with regard to income quartiles and residential areas. There tended to be more patients with CHD in the first- and second-income quartiles. In the control group, 1514094 (50.06%) people lived in metropolitan areas, including Seoul, Gyeonggi-do, and Incheon provinces. Conversely, 113189 (48.75%) patients in the CHD group resided in the metropolitan area. Therefore, the proportion of patients living outside the metropolitan area was relatively higher in the CHD group (especially in Jeolla and Gyeongsang provinces).

There were 114232 (49.2%) male and 117919 (50.8%) female included in the study. Shunt lesions were the most prevalent (85.5%), followed by right-sided lesions, left-sided lesions, cyanotic CHDs, and severe lesions. Aspirin (11.5%) was the most frequently prescribed cardiovascular drug, followed by statin,

Table 1. Comparisons between Groups With or Without CHD

	CHD (+) (n=232203)	CHD (-) (n=3024633)	*p* value
Demographics			
Age, yr	12.8±19.9	13.2±19.8	<0.001
Male	114232 (49.19)	1502010 (49.66)	<0.001
Comorbidity			
HTN	24816 (10.69)	187716 (6.21)	<0.001
DM	5348 (2.30)	75201 (2.49)	<0.001
IHD	14198 (6.11)	70734 (2.34)	<0.001
CHF	17154 (7.39)	33389 (1.10)	<0.001
Hyperlipidemia	29023 (12.50)	285912 (9.45)	<0.001
AF	4440 (1.91)	741 (0.02)	<0.001
Procedure/surgery			
PCI	855 (0.37)	7319 (0.24)	<0.001
CABG	324 (0.14)	244 (0.01)	<0.001
Defibrillator	131 (0.06)	186 (0.01)	<0.001
Pacemaker	836 (0.36)	975 (0.03)	<0.001
Heart valve replacement	4149 (1.79)	673 (0.02)	<0.001
Medications			
Aspirin	26701 (11.5)	123337 (4.08)	<0.001
Clopidogrel	6408 (2.76)	30876 (1.02)	<0.001
Cilostazol	1543 (0.66)	18162 (0.60)	<0.001
Triflusal	545 (0.23)	4561 (0.15)	<0.001
Ticlopidine	175 (0.08)	1261 (0.04)	<0.001
Ticagrelor	93 (0.04)	816 (0.03)	<0.001
Prasugrel	31 (0.01)	319 (0.01)	0.212
Statins	16562 (7.13)	185612 (6.14)	<0.001
Warfarin	9551 (4.11)	6130 (0.20)	<0.001
DOACs	1305 (0.56)	3603 (0.12)	<0.001
Income level			<0.001
Q1	70285 (30.27)	896207 (29.63)	
Q2	78315 (33.73)	1008896 (33.36)	
Q3	44461 (19.15)	606253 (20.04)	
Q4	39134 (16.85)	513023 (16.96)	
Missing value	8 (<0.01)	254 (0.01)	
Region			<0.001
Metropolitan area	113189 (48.75)	1514094 (50.06)	
Gangwon-do	5702 (2.46)	82027 (2.71)	
Chungcheong-do	22378 (9.64)	318138 (10.52)	
Jeolla-do	24672 (10.63)	297392 (9.83)	
Gyeongsang-do	62682 (26.99)	757369 (25.04)	
Jeju-do	2560 (1.10)	36934 (1.22)	
Missing value	1020 (0.44)	18679 (0.62)	

CHD, congenital heart disease; HTN, hypertension; DM, diabetes mellitus; IHD, ischemic heart disease; CHF, congestive heart failure; AF, atrial fibrillation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; DOACs, direct oral anticoagulants.
Values are a mean±standard deviation or n (%). Income level was classified into four groups: Q1, highest 25 percentile income level; Q2, 50.1–75 percentile; Q3, 25.1–50 percentile; Q4, lowest 25 percentile.

https://doi.org/10.3349/ymj.2022.0111

Table 2. The Overall Incidence Rates of Vascular Events and All-Cause Mortality

	CHD (+)	CHD (-)	*p* value
Any stroke			<0.001
Event no.	2283	12637	
Incidence rate per 100000 person years	170.0	69.0	
MI			<0.001
Event no.	970	5752	
Incidence rate per 100000 person years	72.0	31.0	
All-cause mortality			<0.001
Event no.	5848	36871	
Incidence rate per 100000 person years	451.0	205.0	
MACE			<0.001
Event no.	16634	89170	
Incidence rate per 100000 person years	1231.0	483.0	

no., number; CHD, congenital heart disease; MI, myocardial infarction; MACE, major adverse cardiac events.

warfarin, and clopidogrel (Supplementary Table 3, only online). Among the cardiovascular procedures, including PCI, CABG, defibrillator, pacemaker, and heart valve replacement, heart valve replacement (1.8%) was the most frequently performed procedure, followed by stent insertion and pacemaker implantation.

Overall incidence rate of outcomes between CHD and control groups

The overall incidence rates and comparisons of vascular events and all-cause mortality between the two groups are presented in Table 2. Vascular events and all-cause mortality occurred more frequently in the CHD group than in the control group. The overall incidence of all outcomes differed significantly between the two groups (all $p<0.001$). In particular, the overall incidence of any stroke and MACE was three times higher in the CHD group than in the control group.

CHD as a risk factor for vascular events

Fig. 2 shows the Kaplan–Meier survival curves for vascular events and all-cause mortality for the two groups. In the CHD group, the 5-year incidences of stroke, MI, all cause death, and MACE were 0.91%, 0.42%, 2.1%, and 5.8%, respectively. In the control group, the 5-year incidence of stroke, MI, all cause death, and MACE were 0.38%, 0.27%, 0.9%, and 2.3%, respectively. During the entire follow-up period [median follow-up duration, 7.28 (IQR 3.59–8.73) years], event-free survival was significantly lower in the CHD group than in the control group for all outcomes (all $p<0.001$, log-rank test). We investigated the effects of CHD on vascular events and all-cause mortality using multivariate Cox proportional hazards models (Table 3). In the multivariable analysis, CHD was a significant risk factor for vascular events, except all-cause death, after adjusting for several confounding factors.

Subgroup analyses

The incidence of outcomes in adults over 20 years of age according to the age distribution is presented in Supplementary Table 4 (only online). As the event rate of outcomes increased with age, the rate difference between the CHD and control groups diminished, specifically in terms of MI and all-cause death. The age-adjusted event rates of MI and all-cause death were similar between the two groups. In contrast, the age-adjusted event rate of stroke and MACE in the CHD group was approximately two-fold higher than that of the control group, irrespective of sex.

In multivariable analyses evaluating the effect of CHD on outcomes, CHD was a significant risk factor for stroke and MACE, but not for MI or all-cause death (Supplementary Table 5, only online). However, the magnitude of hazard ratio (HR) for the CHD group aged >20 years with stroke and MACE was reduced compared with the HRs in the whole CHD population.

DISCUSSION

To the best of our knowledge, this nationwide study is the first to investigate the epidemiological characteristics, as well as the burden of vascular events and all-cause mortality, in Korean patients with CHD using the Korean NHIS data. This is also the first study to confirm that CHD can be an important predictor of vascular events in the Korean population. The prevalence of comorbidities, number of cardiac procedures, and use of antithrombotic agents and statins were higher in CHD patients than in the age- and sex-matched general population. The overall incidence of all outcomes differed significantly between the two groups. Furthermore, in a subgroup analysis of the adult population over 20 years of age, the age-adjusted event rates of stroke and MACE were two-fold higher in the CHD group than in the control group. However, there were no significant differences in the age-adjusted event rates of MI and all-cause death. In multivariate analysis of the adult population, CHD was a significant risk factor for stroke and MACE, while the risk decreased for MI and all-cause death.

In our study of patients with CHD, extracted from the 2006 to 2017 NHIS dataset, the incidence rates of all vascular events and all-cause mortality in patients with CHD were more than double of those in the general population. In particular, the incidence of stroke and MACE was three times higher. Recently, there have been nationwide studies on the incidence of vascular events and mortality in patients with CHD in several countries. In Sweden, in a study targeting all age groups (year of birth±SD: 1990.2±22.5, mean follow-up time: 25.1±22.0 years), the incidence of ischemic stroke was 1.48 per 1000 person years, five times higher than that of the general population.[16] Another Swedish study demonstrated that the incidence of MI in adult patients with CHD aged >40 years was 3.83 per 1000 person years, which was 1.6 times greater than that of the general population.[18] In a Canadian study targeting adult patients with CHD (mean age 49.9 years), the age-adjusted incidence of stroke was reported as 1.19–1.66 per 1000 person years and the incidence rate of stroke in CHD patients under 55 years of age was more than five times higher than that of the general population and more than two times higher in

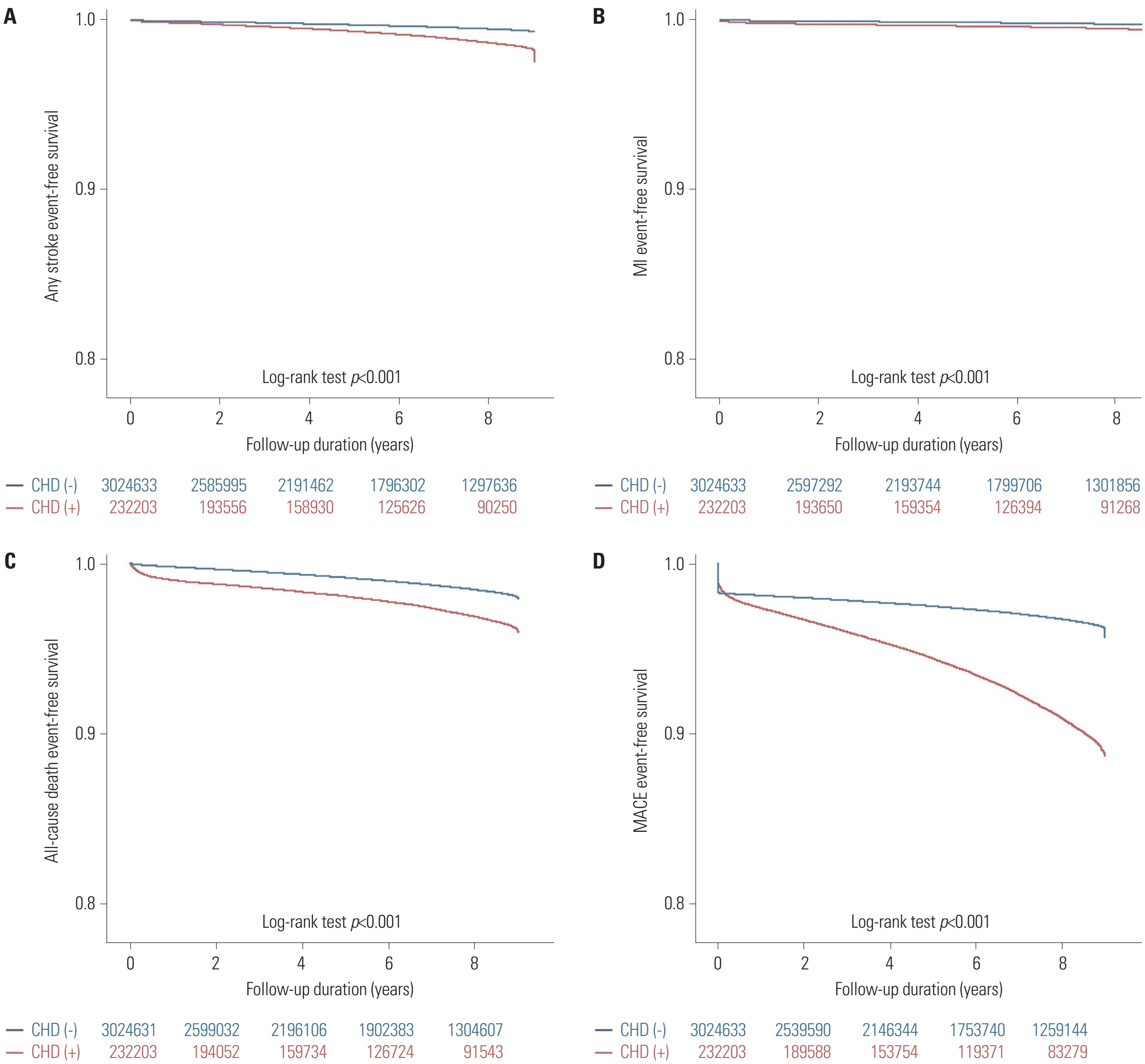

Fig. 2. Kaplan–Meier curves for groups with and without CHD. (A) Any stroke. (B) Myocardial infarction (MI). (C) All-cause mortality. (D) Major adverse cardiovascular events (MACE).

Table 3. Multivariable Analysis for Vascular Events and All-Cause Mortality in the Overall Population

	Any stroke		MI		All-cause mortality		MACE	
	SHR (95% CI)	*p* value	SHR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
CHD	1.95 (1.89–2.00)	<0.001	1.79 (1.74–1.84)	<0.001	1.02 (1.00–1.05)	0.08	1.41(1.38–1.44)	<0.001

MI, myocardial infarction; MACE, major adverse cardiac events; CHD, congenital heart disease; SHR, sub-distribution hazard ratio; DM, diabetes mellitus; HTN, hypertension; CHF, congestive heart failure; AF, atrial fibrillation; CI, confidence interval.
Variables with $p<0.05$, in univariable analyses were entered into the multivariable model. Any stroke and all-cause mortality were adjusted for age, sex, DM, HTN, hyperlipidemia, ischemic heart disease, CHF, AF, CHD, antiplatelet agents, anticoagulants, statins, valve replacement, stent insertion, bypass graft, defibrillator, and pacemaker use. MI and MACE were adjusted for age, sex, DM, HTN, hyperlipidemia, CHF, AF, CHD, antiplatelet agents, anticoagulants, statins, valve replacement, stent insertion, bypass graft, defibrillator, and pacemaker use.

https://doi.org/10.3349/ymj.2022.0111

those older than 55 years.[17] Fox, et al.[19] reported a 19-fold higher risk of stroke among patients with CHD under the age of 20 years living in Northern California. With regards to the risk of vascular outcomes and mortality, our study demonstrated that the HRs of any stroke, MI, and all-cause mortality in CHD were 1.94, 1.79, and 1.72, respectively, and the HR of MACE was 1.77 in patients with CHD. A nationwide study conducted in Denmark reported that the HR of CHD for MI was 2.00.[20] Additionally, in a study from Taiwan, the HR for acute coronary syndrome was reported as 2.89, and that for stroke was 2.16 in patients with CHD.[21] The incidence of MACE was estimated to be fourfold higher in the CHD group than in the general population.[21] A second study from Taiwan reported that the mortality rate of adult patients with CHD was 1.3 times higher than that of the general population and 3.2 times higher in patients with severe CHD.[22] Another study of children with CHD born after the 1980s estimated the mortality rate to be 17.7 times higher than that of the general population, despite an increased survival rate.[23]

Although this study cannot scrutinize the reason why MACE occurred more frequently in patients with CHD, there are some plausible explanations. First, they are prone to have different coronary artery anatomy, inflammatory changes of the coronary arteries from the surgical procedure or abnormal anatomy of the CHD itself, reperfusion injury during surgery, and aortopathy including dilated aorta and increased aortic stiffness, leading to premature atherosclerotic CAD.[24] Second, our study established that the prevalence of comorbidities, including HTN, IHD, CHF, hyperlipidemia, and AF, except DM, is much higher in the CHD group than in the control group. These are important cardiovascular risk factors that can accelerate atherosclerotic changes along with the effect of CHD and ultimately lead to the development of vascular events in vascular beds. Third, children with CHD who have undergone repair surgery can be susceptible to early atherosclerosis due to limited physical activity, with a lack of exercise being a risk factor for atherosclerosis. Finally, the pathophysiology of CHF in patients with CHD is different from that of the general population.[5] CHD populations may have a systemic right ventricle, a failing subpulmonic ventricle, or a single ventricle physiology.[5] Moreover, they are susceptible to CHF due to chronic pressure/volume overload and myocardial injury.[5,21] The occurrence of arrhythmia becomes frequent in them due to congenital and acquired factors, and arrhythmia is a risk factor for heart failure.[5,21,25] These findings can affect the occurrence of cardiovascular events and vascular death.

The disparity in incidence and HRs for each complication, reported by these countries, could be associated with the variability in health care policy and systems, the heterogeneity of patient characteristics (age, comorbidities, ethnicity), and differences in study design and methods. Taken together with these findings, it is clear that the incidence and risk of vascular events are higher in CHD patients than in the general population. We performed subgroup analyses on adult patients aged >20 years. The incidence of events in the CHD and control groups showed a more significant difference as they were younger, whereas the difference diminished in the older population. In adult patients with CHD, age-adjusted event rates for MI and all-cause death were similar to those of the general population aged >20 years, whereas age-adjusted event rates for stroke and MACE were more than two times higher than those of the general population. In multivariable analyses, CHD was found to be a significant risk factor for stroke and MACE. Due to the influence of CHD as a predictor of reversed MI and all-cause mortality, CHD is likely to have protective effects against MI and all-cause mortality. In addition, the magnitude of HR for the CHD group aged >20 years with stroke and MACE was reduced, compared with that in the whole CHD population. These results for the adult population may be influenced by the fact that the average age of patients with CHD in this study was relatively younger than that of other countries, and the follow-up duration was relatively short. Furthermore, some patients with CHD, if the severity of CHD was higher, may have already experienced these events, including MI and all-cause death, before they reached adulthood. Therefore, the incidence of these events in ACHD may be rather low. On the other hand, the general population is more susceptible to the high risk of these events with advancing years. Nevertheless, the risk of stroke and MACE increased in ACHD patients in this study. Therefore, the prevention of vascular events, including stroke, is a life-long issue for patients with CHD.

Previous studies have reported that patients with CHD are at high risk of comorbidities and metabolic syndrome.[26,27] Additionally, it has been reported that patients with CHD are at high risk of stroke and coronary artery disease, and male sex, CHF, HTN, DM, AF, recent MI, and some cardiac characteristics (previous shunts, septal defects, mechanical valves, and cyanosis) have been reported as risk factors for these vascular events.[15,17,21,28-31] In the present study, CHD patients had a high incidence of comorbidities, such as HTN, AF, CHF, and IHD, but not for DM. The higher incidences of these comorbidities in CHD patients could imply that these patients are more susceptible to developing these vascular events than the general population. Further studies are warranted to identify high-risk patients with CHD and related risk factors, such as CHD characteristics and types, for these events.

This study has some limitations. First, this study was based on NHIS data, which have an inherent possibility of information bias, and the ICD-10 code may not fully reflect the actual diagnoses of patients. Second, the NHIS data have limitations in obtaining detailed information about the patient's clinical status or lifestyle habits, such as diet, alcohol use, and smoking status. Third, the median follow-up period (7.28 years) in this study was much shorter than that in previous studies and hampered the ability to observe the long-term effects of CHD.[16,18,21,23] However, we included 232219 patients with CHD, which was the largest case population used to evaluate the incidence of vascular events in patients with CHD. Fourth, there was a significant difference between the CHD and control groups in terms of income distribution and residential area, but this may be attributed to chance rather than a meaningful difference. This tendency is one of the common errors that can occur in a study with a large sample size, and cautious interpretation is required. Fifth, we did not consider a look-back period when identifying comorbidities, therefore, we could not acquire information regarding the diagnosis time and exposure time of comorbidities. Finally, CHD is a composite entity comprising diverse and heterogeneous congenital diseases. Therefore, pathophysiologic mechanisms and specific cardiac operations or procedures [e.g., atrial septal defect (ASD) patch/device closure, ventricular septal defect closure, Rastelli operation, arterial switch operation, and Fontan procedure] could differ and affect vascular events according to CHD. Indeed, ASD closure could lead to a reduction in the risk of stroke in the long term, although the perioperative stroke risk may be higher. However, this study did not consider the effects of specific diseases. These effects can be extrapolated from additional studies focusing on specific diseases.

In conclusion, this first nationwide study demonstrated that Korean patients with CHD have a high incidence of comorbidities, vascular events, and mortality. CHD has been established as an important predictor of cardiovascular events. In adult patients with CHD, CHD is still sustained as an important predictor of stroke and composite vascular events, despite the impact of CHD on vascular events being reduced or reserved according to the type of event. Further studies are warranted to identify high-risk patients with CHD and related factors to prevent vascular events.

ACKNOWLEDGEMENTS

This research was supported by the Korean Cardiac Research Foundation (202003-01).

Data for this study were obtained from The Korean National Health Insurance Service (NHIS).

Jin-Man Jung has received the following: lecture honoraria from Pfizer, Sanofi-Aventis, Otsuka, Dong-A, and Hanmi Pharmaceutical Co., Ltd., and Boryung Pharmaceutical Co., Ltd.; a study grant from Il-dong and Cheiljedang Pharmaceutical Co., Ltd.; and consulting fees from Daewoong Pharmaceutical Co., Ltd.

AUTHOR CONTRIBUTIONS

Conceptualization: Woo-Keun Seo and Hong Ju Shin. Data curation: Jin-Man Jung and Jongun Choi. Formal analysis: Jin-Man Jung and Jongun Choi. Funding acquisition: Jin-Man Jung and Hong Ju Shin. Investigation: Jin-Man Jung and Jongun Choi. Methodology: Jue Seong Lee, Jin-Man Jung, and Hong Ju Shin. Project administration: Woo-Keun Seo and Hong Ju Shin. Resources: Woo-Keun Seo. Software: Jue Seong Lee, Jin-Man Jung, and Hong Ju Shin. Supervision: Woo-Keun Seo and Hong Ju Shin. Validation: Jue Seong Lee and Jin-Man Jung. Visualization: Jue Seong Lee, Jin-Man Jung, and Hong Ju Shin. Writing—original draft: Jue Seong Lee and Jin-Man Jung. Writing—review & editing: Woo-Keun Seo and Hong Ju Shin. Approval of final manuscript: all authors.

ORCID iDs

Jue Seong Lee	https://orcid.org/0000-0003-1803-4682
Jin-Man Jung	https://orcid.org/0000-0003-0557-6431
Jongun Choi	https://orcid.org/0000-0001-7356-6740
Woo-Keun Seo	https://orcid.org/0000-0002-4004-8434
Hong Ju Shin	https://orcid.org/0000-0002-0731-3523

REFERENCES

1. van der Linde D, Konings EE, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, et al. Birth prevalence of congenital heart disease worldwide: a systematic review and meta-analysis. J Am Coll Cardiol 2011;58:2241-7.
2. Liu Y, Chen S, Zühlke L, Black GC, Choy MK, Li N, et al. Global birth prevalence of congenital heart defects 1970-2017: updated systematic review and meta-analysis of 260 studies. Int J Epidemiol 2019;48:455-63.
3. Lytzen R, Vejlstrup N, Bjerre J, Petersen OB, Leenskjold S, Dodd JK, et al. Live-born major congenital heart disease in Denmark: incidence, detection rate, and termination of pregnancy rate from 1996 to 2013. JAMA Cardiol 2018;3:829-37.
4. Moons P, Bovijn L, Budts W, Belmans A, Gewillig M. Temporal trends in survival to adulthood among patients born with congenital heart disease from 1970 to 1992 in Belgium. Circulation 2010;122:2264-72.
5. Baumgartner H, De Backer J, Babu-Narayan SV, Budts W, Chessa M, Diller GP, et al. 2020 ESC guidelines for the management of adult congenital heart disease. Eur Heart J 2021;42:563-645.
6. Hoffman JIe. The global burden of congenital heart disease. Cardiovasc J Afr 2013;24:141-5.
7. Lee JY. Global burden of congenital heart disease: experience in Korea as a potential solution to the problem. Korean Circ J 2020;50:691-4.
8. Shin HJ, Park YH, Cho BK. Recent surgical outcomes of congenital heart disease according to Korea Heart Foundation data. Korean Circ J 2020;50:677-90.
9. Jang SY, Seo SR, Moon JR, Cho EJ, Kim E, Chang SA, et al. Prevalence and mortality of congenital heart disease in Korean adults. Medicine (Baltimore) 2018;97:e11348.
10. McHutchison CA, Backhouse EV, Cvoro V, Shenkin SD, Wardlaw JM. Education, socioeconomic status, and intelligence in childhood and stroke risk in later life: a meta-analysis. Epidemiology 2017;28:608-18.
11. Schröder SL, Richter M, Schröder J, Frantz S, Fink A. Socioeconomic inequalities in access to treatment for coronary heart disease: a systematic review. Int J Cardiol 2016;219:70-8.
12. Afilalo J, Therrien J, Pilote L, Ionescu-Ittu R, Martucci G, Marelli AJ. Geriatric congenital heart disease: burden of disease and predictors of mortality. J Am Coll Cardiol 2011;58:1509-15.
13. Tutarel O, Kempny A, Alonso-Gonzalez R, Jabbour R, Li W, Uebing A, et al. Congenital heart disease beyond the age of 60: emergence of a new population with high resource utilization, high morbidity, and high mortality. Eur Heart J 2014;35:725-32.
14. Lee SH, Kim KY, Lee JW, Park SJ, Jung JM. Risk of ischaemic stroke in patients with transient global amnesia: a propensity-matched cohort study. Stroke Vasc Neurol 2022;7:101-7.
15. Wang T, Chen L, Yang T, Huang P, Wang L, Zhao L, et al. Congeni-

tal heart disease and risk of cardiovascular disease: a meta-analysis of cohort studies. J Am Heart Assoc 2019;8:e012030.
16. Giang KW, Fedchenko M, Dellborg M, Eriksson P, Mandalenakis Z. Burden of ischemic stroke in patients with congenital heart disease: a nationwide, case-control study. J Am Heart Assoc 2021;10: e020939.
17. Lanz J, Brophy JM, Therrien J, Kaouache M, Guo L, Marelli AJ. Stroke in adults with congenital heart disease: incidence, cumulative risk, and predictors. Circulation 2015;132:2385-94.
18. Fedchenko M, Mandalenakis Z, Giang KW, Rosengren A, Eriksson P, Dellborg M. Long-term outcomes after myocardial infarction in middle-aged and older patients with congenital heart disease-a nationwide study. Eur Heart J 2021;42:2577-86.
19. Fox CK, Sidney S, Fullerton HJ. Community-based case-control study of childhood stroke risk associated with congenital heart disease. Stroke 2015;46:336-40.
20. Olsen M, Marino B, Kaltman J, Laursen H, Jakobsen L, Mahle W, et al. Myocardial infarction in adults with congenital heart disease. Am J Cardiol 2017;120:2272-7.
21. Lin YS, Liu PH, Wu LS, Chen YM, Chang CJ, Chu PH. Major adverse cardiovascular events in adult congenital heart disease: a population-based follow-up study from Taiwan. BMC Cardiovasc Disord 2014;14:38.
22. Wu MH, Lu CW, Chen HC, Kao FY, Huang SK. Adult congenital heart disease in a nationwide population 2000-2014: epidemiological trends, arrhythmia, and standardized mortality ratio. J Am Heart Assoc 2018;7:e007907.
23. Mandalenakis Z, Giang KW, Eriksson P, Liden H, Synnergren M, Wåhlander H, et al. Survival in children with congenital heart disease: have we reached a peak at 97%? J Am Heart Assoc 2020;9: e017704.
24. Niwa K. Metabolic syndrome and coronary artery disease in adults with congenital heart disease. Cardiovasc Diagn Ther 2021;11:563-76.
25. Waldmann V, Laredo M, Abadir S, Mondésert B, Khairy P. Atrial fibrillation in adults with congenital heart disease. Int J Cardiol 2019; 287:148-54.
26. Moon JR, Song J, Huh J, Kang IS, Park SW, Chang SA, et al. Analysis of cardiovascular risk factors in adults with congenital heart disease. Korean Circ J 2015;45:416-23.
27. Billett J, Cowie MR, Gatzoulis MA, Vonder Muhll IF, Majeed A. Comorbidity, healthcare utilisation and process of care measures in patients with congenital heart disease in the UK: cross-sectional, population-based study with case-control analysis. Heart 2008;94: 1194-9.
28. Pillutla P, Shetty KD, Foster E. Mortality associated with adult congenital heart disease: trends in the US population from 1979 to 2005. Am Heart J 2009;158:874-9.
29. Bokma JP, Zegstroo I, Kuijpers JM, Konings TC, van Kimmenade RRJ, van Melle JP, et al. Factors associated with coronary artery disease and stroke in adults with congenital heart disease. Heart 2018;104:574-80.
30. Hoffmann A, Chockalingam P, Balint OH, Dadashev A, Dimopoulos K, Engel R, et al. Cerebrovascular accidents in adult patients with congenital heart disease. Heart 2010;96:1223-6.
31. Pedersen MGB, Olsen MS, Schmidt M, Johnsen SP, Learn C, Laursen HB, et al. Ischemic stroke in adults with congenital heart disease: a population-based cohort study. J Am Heart Assoc 2019;8: e011870.