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건강보험공단 표본 코호트 자료를 이용한, 국내 심방세동 환자의 사망률과 사망 원인에 관한 연구

Mortality and causes of death in patients with atrial fibrillation: A nationwide population-based study

2019 년 2 월

서울대학교 대학원
의학과 임상의과학 전공
이의재

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이 논문을 의학석사 학위논문으로 제출함

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Abstract

Mortality and causes of death in patients with atrial fibrillation: A nationwide population-based study

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Background: Patients with atrial fibrillation (AF) are known to have higher risk of mortality. There is a paucity information regarding the impact of AF on mortality risk stratified by age, sex, and detailed cause of death in a population-based study.

Methods: In Korean National Health Insurance Service-National Sample Cohort, 15,411 patients with AF were enrolled, and causes of death were identified according to ICD-10 codes.

Results: From 2002 to 2013, a total of 4,479 (29%) deaths were confirmed, and crude mortality rate (MR) for all-cause death was 63.3 per 1,000 patient-years. Patients with AF were at 3.7-fold increased risk of all-cause death compared with general population. Standardized mortality ratio (SMR) for all-cause death was highest in those with young age and attenuated with increasing age [SMR 21.93, 95% confidence interval (CI) 7.60-26.26 in <20 years; SMR 2.77, 95% CI 2.63-2.91 in ≥80 years]. Women with AF exhibited a greater excess mortality risk than men (SMR 3.81, 95% CI 3.65-3.98 in women;

SMR 3.35, 95% CI 3.21-3.48 in men). Cardiovascular disease was the leading cause of death (38.5%), and cerebral infarction was the most common specific disease. Patients with AF had about 5 times increased risk of death for cardiovascular disease compared with general population.

Conclusions: Patients with AF had 4 times increased risk of mortality compared to general population. However, the impact of AF on mortality attenuated with age, and men. Cerebral infarction was the most common cause of death, and further attention should be made to reduce the risk of stroke.

Keywords: atrial fibrillation; mortality rate; standardized mortality ratio; cause of death; population-based study; epidemiology; Korean National Health Insurance Service-National Sample Cohort

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia, showing a gradually increasing incidence and prevalence globally [1, 2]. AF is associated with an increased risk of mortality after adjusting for cardiovascular comorbidities [3]. Previous studies have reported that AF is closely associated with an increased risk of all-cause and cardiovascular mortality [4-6]. However, most previous studies that have investigated the prognosis of AF have been performed in Western populations [4-8], and a few studies have reported mortality rates associated with AF in Asians [9-11]. In a prospective registry of 46 countries across 8 geographical regions, 1-year mortality in South America and Africa was twice that in North America, Western Europe, and Australia, suggesting an inter-regional and ethnic difference in mortality in patients with AF [9]. Considering the differences between Asians and Westerners in terms of life expectancy, prevalence of cardiometabolic risk factors, availability and types of medical, and social welfare systems, the prognostic significance of AF on mortality understandably differs between the 2 populations.

A recent meta-analysis evaluated the differential prognostic effects of AF based on sex indicating that AF was significantly associated with a higher risk of all-cause and cardiovascular mortality in women than in men [4]. However, it is unclear whether the effect of AF on mortality varies with age. Additionally, no population-based study has thoroughly investigated the cause of death in patients with AF. Therefore, we investigated the mortality patterns and closely analyzed the cause of death in patients with AF using a nationwide population-based cohort.

Materials and methods

Database

The Korean National Universal Healthcare program operated by the National Health Insurance Service (NHIS) is a mandatory medical care system intended to benefit the Korean population (approximately 50 million people). The NHIS stores and manages an accurate database comprising healthcare practices and prescriptions in Korea. The National Health Insurance Service-National Sample Cohort (NHIS-NSC) is a population-based cohort created by the NHIS. The NHIS-NSC provides medical researchers with representative and effective information concerning citizens' healthcare system utilization and health examinations. The cohort comprises 1,025,340 individuals that represented 2.2% of all Korean population in 2002. The subject have been selected through systematic stratified random sampling with 1,476 strata that consisted of 18 groups according to age, 2 groups according to sex, and 41 groups according to subject's income level. Representativeness of cohort assessed by examining whether a 95% confidence interval for the sample's average total annual medical expenses contained the population average. In addition, the cohort was compared to the population according to residence distribution across 16 regions in Korea. Detailed information regarding NHIS-NSC has been described elsewhere [12, 13]. We were approved to use the database released by the NHIS in 2014, which included patients observed between 2002 and 2013.

Study population

According to the revised 10th International Statistical Classification of Diseases (ICD-10) codes, AF was defined as I48 to include patients requiring ≥2 outpatient visits or ≥1 hospitalization per year. To ensure that the study included only those with nonvalvular AF, we excluded patients diagnosed with mitral stenosis (I50, I52, and I59) or with pre-existing

mechanical heart valves (Z952–Z945). Patients with comorbidities such as hypertension (I10-I15), diabetes mellitus (E11-E14), congestive heart failure (I50), stroke (I63 or I64), transient ischemic attack (TIA) (G458 or G459), thromboembolism (I74), myocardial infarction (I21 or I22), and/or peripheral artery disease (I70 or I73) were summarized in Table 1, and validated in previous studies [2, 14-17]. The congestive heart failure/left ventricular dysfunction, hypertension, ≥75 years, diabetes mellitus, previous stroke or TIA or thromboembolism, vascular disease, aged 65 to 74 years, sex female (CHA_2DS_2-VASc) score was calculated for each patient by assigning 1 point each for age between 65 and 74 years, female sex, and the presence of hypertension, diabetes mellitus, heart failure, and vascular disease (prior myocardial infarction or peripheral artery disease), and adding 2 points each for a history of stroke/TIA/thromboembolism or age ≥75 years [18].

Patients were stratified into 10-year age groups; young (<20) and old (>80) patients were grouped together because of their relatively small numbers. The enrollment date of each patient with AF was the first date of claims for AF in the database. All patients underwent follow-up from the date of the enrollment of the study to the end of 2013 or a day of disqualification due to death or emigration.

Table 1. International Classification of Diseases (ICD) codes used in this study for defining atrial fibrillation and patients' baseline comorbidities.

Variables	ICD-10 codes	Diagnostic definition
Atrial fibrillation	Inclusion: I48 Exclusion: I50, I52, I59, Z952-Z954	≥1 admission or ≥2 outpatient department visits in a year
Hypertension*	I10-I15	≥1 admission or ≥2 outpatient department visits AND Use of ≥1 anti-hypertensive medication (thiazide, loop diuretics, aldosterone antagonist, alpha blocker, beta blocker, calcium channel blocker, angiotensin converting enzyme inhibitor, and angiotensin II receptor blocker)
Diabetes mellitus*	E11-E14	≥1 admission or ≥2 outpatient department visits AND Use of anti-diabetic medication (sulfonyurea, metformin, meglitinide, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, alpha-glucosidase inhibitor, and insulin)
Congestive heart failure	I50	≥1 admission or ≥1 outpatient department visit

Ischemic heart disease	I20-I25	≥1 admission or ≥2 outpatient department visits
Myocardial infarction	I21, I22	≥1 admission or ≥1 outpatient department visit
Peripheral artery disease	I70, I73	≥1 admission or ≥1 outpatient department visits
Stroke	I63, I64	≥1 admission or ≥1 outpatient department visits
Transient ischemic attack	G458, G4599	≥1 admission or ≥1 outpatient department visits
Thromboembolism	I74	≥1 admission or ≥1 outpatient department visits
Dyslipidemia	E78	≥1 admission or ≥1 outpatient department visit
Chronic lung disease	J41-J44	≥1 admission or ≥1 outpatient department visit
End-stage renal disease	N18, N19, Z49, Z905, Z94, Z992	≥2 dialysis (hemodialysis or peritoneal dialysis)
Cancer	Any C	≥1 admission or ≥1 outpatient department visit

* Hypertension and diabetes mellitus were identified to have the diagnosis when patients had ≥1 admission or ≥2 outpatient department visits and relevant prescription record for preventing overestimation of diagnosis.

Mortality and causes of death

We used the mortality database provided by Statistics Korea, a government agency. This mortality database includes death-related data such as age at the time of death, causes, date and place of death. The causes of death were coded based on the Korean Standard Classification of Diseases and Causes of Death, which in turn is based on the ICD-10 system. The 2 datasets were matched by a resident registration number, which is a unique personal identification system used in Korea. Finally, all provided data were de-identified.

Statistical Analysis

The number of deaths and person-years of follow-up were analyzed, and mortality rates were calculated based on the number of deaths per 1,000 person-years. The standardized mortality ratio (SMR) was used to compare mortality rates with the general population. SMR is the ratio of the observed deaths in the population with AF to the expected deaths based on data from the general Korean population. Expected mortality was calculated by dividing the number of deaths in the general population between 2002 and 2013 by an average of midyear population in the same period from the Korean Statistical Information Service (Statistics Korea, Causes of death statistics, 2002-2013). Causes of death, cause-specific mortality rates and cause-specific SMRs were computed based on ICD-10 codes. SMR and 95% confidence intervals (CI) were calculated using Byar approximation [19]. Survival analysis of patients with AF based on the CHA_2DS_2-VASc score was performed using the Kaplan-Meier method. All statistical analyses were performed using the SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Ethical statement

This study was approved by NHIS Review Committee (2017-2-287) and was exempt from review by the Seoul National University Hospital Institutional Review Board (1612-037-812). The subjects were not identified because the database was de-identified and anonymized from the beginning. Therefore, informed consent could not be obtained.

Results

Patient characteristics

Among the 1,025,340 individuals whose information was available in the NHIS-NSC database, we identified 15,411 patients with AF between 2002 and 2013. Baseline characteristics of patients with AF have been shown in Table 2. The mean age was 63.9 ± 15.9 years, and 8,226 (53.4%) patients were men. Two-thirds of patients with AF were aged ≥60 years (n=10,292, 66.7%) and 16.9% of patients were aged <50 years (n=1,232). The mean CHA_2DS_2-VASc score was 2.9±1.9. At the time of identification, we observed 5,363 (34.8%), 1,353 (8.8%), and 3,674 (23.8%) patients with ischemic heart disease, myocardial infarction, and congestive heart failure, respectively. A previous history of stroke or TIA was noted in 2,384 (15.5%) patients. Approximately 18% of patients with AF received oral anticoagulant (OAC) and 11% of patients received antiarrhythmic drugs in the same year as AF diagnosis. Patients with OAC was older than non-OAC patients (65.3 ± 12.7 vs. 63.6 ± 16.6 years, $p<0.001$) and had higher mean CHA_2DS_2-VASc score (3.5 ± 1.9 vs. 2.8 ± 2.0, $p<0.001$). Patients with

antiarrhythmic drugs (AAD) had more OAC therapy than those without AAD (32.1% vs. 16.1%, p<0.001).

Table 2. Baseline characteristics of patients with atrial fibrillation in National Health Insurance-National Sample Cohort database.

	Total (N=15,411)	Men (N=8,226)	Women (N=7,185)
Age, years	63.9±15.9	61.9±15.7	66.2±15.9
<20	215 (1.4)	136 (1.7)	79 (1.1)
20-29	348 (2.3)	192 (2.3)	156 (2.2)
30-39	669 (4.3)	385 (4.7)	284 (4.0)
40-49	1,372 (8.9)	873 (10.6)	499 (6.9)
50-59	2,515 (16.3)	1,567 (19.0)	948 (13.2)
60-69	3,875 (25.1)	2,201 (26.8)	1,674 (23.2)
70-79	4,118 (26.7)	2,014 (24.5)	2,104 (29.3)
≥80	2,299 (14.9)	858 (10.4)	1,441 (20.1)
Body mass index (kg/m^2)*	24.24±3.39	24.15±3.24	24.36±3.58
Smoking status*			
Non-smoker	4,179 (67.4)	1,699 (47.3)	2480 (94.9)
Ex-smoker	879 (14.2)	840 (23.4)	39 (1.5)
Current smoker	1,145 (18.5)	1,051 (29.3)	94 (3.6)
CHA_2DS_2-VASc score	2.9±1.9	2.3±1.7	3.7±1.9
Hypertension	9,893 (64.2)	5,141 (62.5)	4,752 (66.1)

Diabetes mellitus	3,370 (21.9)	1,795 (21.8)	1,575 (21.9)
Congestive heart failure	3,674 (23.8)	1,748 (21.3)	1,926 (26.8)
Ischemic heart disease	5,363 (34.8)	2,883 (35.1)	2,480 (34.5)
Myocardial infarction	1,353 (8.8)	771 (9.4)	582 (8.1)
Peripheral artery disease	1,820 (11.8)	957 (11.6)	863 (12.0)
Stroke or TIA	2,384 (15.5)	1,217 (14.8)	1,167 (16.2)
Dyslipidemia	6,482 (42.1)	3,341 (40.6)	3,141 (43.7)
Chronic lung disease	3,476 (22.6)	1,979 (24.1)	1,497 (20.8)
End-stage renal disease	220 (1.4)	128 (1.6)	92 (1.3)
Cancer	2,173 (14.1)	1,372(16.7)	801 (11.2)
Oral anticoagulant	2,759 (17.9)	1,565 (19.0)	1,194 (16.6)
Antiarrhythmic drugs (Ic + III)	1,769 (11.5)	1,068 (13.0)	701 (9.8)

Data are expressed as the mean ± standard deviation or as the number (percentage).

*Only 6,203 patients (3,590 men and 2,613 women) had information of body weight, height and smoking status.

AF, atrial fibrillation; NHIS-NSC, National Health Insurance Service-National Sample Cohort; TIA, transient ischemic attack

All-cause mortality in patients with atrial fibrillation

We observed 4,479 deaths during a total of 70,791 person-years of follow-up. The age-specific mortality rate and SMR for all-cause death were presented in Figure 1 and age- and sex-specific mortality rate and SMR for all-cause death have been shown in Table 3. Overall, in patients with AF, the crude mortality rate for all-cause death was 63.3 per 1,000 person-years. Patients with AF demonstrated a 3.67-fold higher risk of all-cause death than that in an age- and sex-matched general population (SMR 3.67, 95% CI 3.56–3.78).

Table 3. The age- and sex- specific all-cause mortality rate and standardized mortality ratio of patients with atrial fibrillation.

	Total					Men				Women			
	N	Death	P-Y	MR[a]	SMR (95% CI)	Death	P-Y	MR	SMR (95% CI)	Death	P-Y	MR	SMR (95% CI)
<20	215	9	1,321	6.8	21.93 (7.60-36.26)	6	841	7.1	19.50 (3.90-35.10)	3	479	6.3	25.02 (0.00-53.34)
20s	348	11	2,240	4.9	9.04 (3.70-14.39)	5	1,159	4.3	6.50 (0.80-12.20)	6	1,081	5.5	13.44 (2.69-24.20)
30s	669	36	4,018	9.0	10.26 (6.91-13.61)	22	2,225	9.9	8.93 (5.20-12.67)	14	1,792	7.8	12.37 (5.89-18.86)
40s	1,372	95	8,223	11.6	5.73 (4.58-6.88)	70	5,101	13.7	4.79 (3.67-5.91)	25	3,121	8.0	7.02 (4.27-9.78)
50s	2,515	333	13,438	24.8	5.89 (5.26-6.52)	246	8,180	30.1	4.80 (4.20-5.39)	87	5,257	16.5	7.74 (6.12-9.37)
60s	3,875	949	20,460	46.4	4.77 (4.47-5.08)	618	11,096	55.7	3.90 (3.59-4.21)	331	9,363	35.4	6.35 (5.66-7.03)
70s	4,118	1,618	15,624	103.6	3.78 (3.59-3.96)	883	6,972	126.6	3.22 (3.01-3.43)	735	8,652	85.0	4.40 (4.08-4.72)
≥80	2,299	1,428	5,468	261.1	2.77 (2.63-2.91)	577	1,887	305.7	2.58 (2.37-2.79)	851	3,581	237.6	2.81 (2.62-3.00)
Overall	15,411	4,479	70,791	63.3	3.67 (3.56-3.78)	2427	37,462	64.8	3.35 (3.21-3.48)	2,052	33,329	61.6	3.81 (3.65-3.98)

[a]MR was presented as the number of deaths per 1,000 person-year.

AF, atrial fibrillation; CI, confidence interval; MR, mortality rate; P-Y, person-year; SMR, standardized mortality ratio.

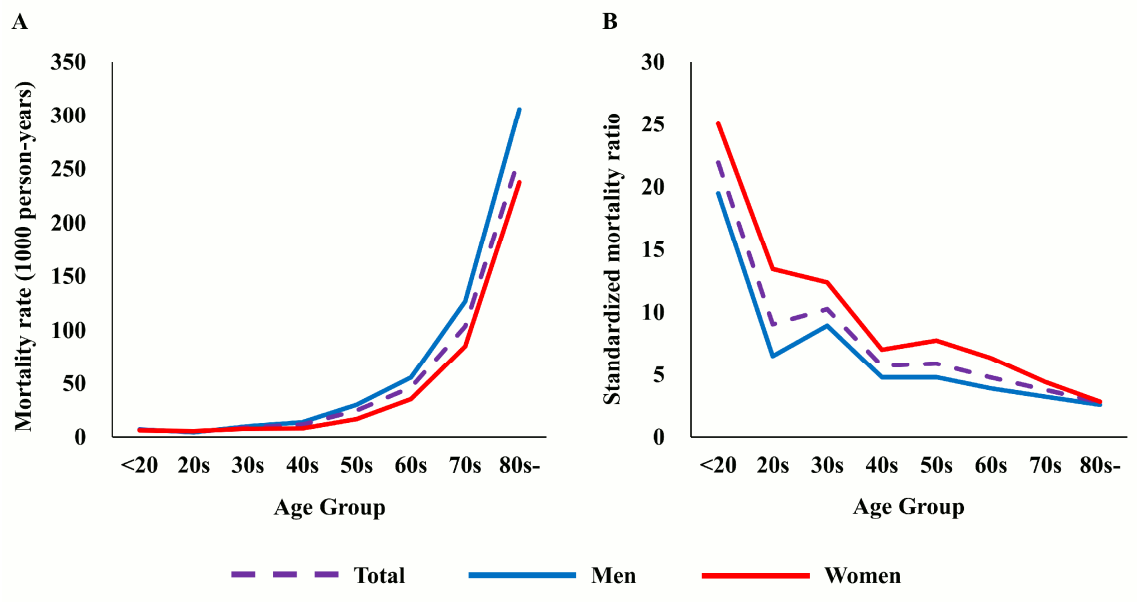

Figure 1. Age-specific mortality rates and standardized mortality ratios (SMR) of patients with atrial fibrillation (AF).

(A) The mortality rates of patients with AF increased with age. Male patients with AF showed higher mortality rates than female patients with AF. (B) The SMR of patients with AF decreased with age. Female patients with AF showed higher SMR than male patients with AF.

The crude mortality rate was higher in men than in women (64.8 vs. 61.6 per 1,000 person-years, respectively). We investigated the sex-specific SMR to determine the prognostic significance of AF based on sex. Women showed a higher SMR than that in men. Women with AF showed a 3.81-fold higher mortality risk than that noted in women belonging to the general population (SMR 3.81, 95% CI 3.65–3.98); however, men showed a 3.35-fold increased risk (SMR 3.35, 95% CI 3.21–3.48). The age-specific all-cause mortality rate increased with age, particularly beyond the age of 60 years (from 4.9 per 1,000 person-years in those in the 20s to 261.1 per 1,000 person-years in

those aged ≥80 years). Regarding age-specific SMR, SMR was the highest in the younger age groups and decreased with increasing age (SMR 21.93, 95% CI 7.60–26.26 in those aged <20 years vs. SMR 2.77, 95% CI 2.63-2.91 in those aged ≥80 years, Table 3). All-cause SMRs were higher in women than in men across all age groups. The mortality in patients with OAC was lower than that in patients without OAC even the patients with OAC are old and have higher CHA_2DS_2-VASc score (23.0% vs. 30.4%, p<0.001). The mortality rate in patients with AAD was lower compared to those in patients without AAD (14.5% vs. 31.0%, p<0.001). The CHA_2DS_2-VASc score showed a close correlation with overall survival in both men and women (Figure 2).

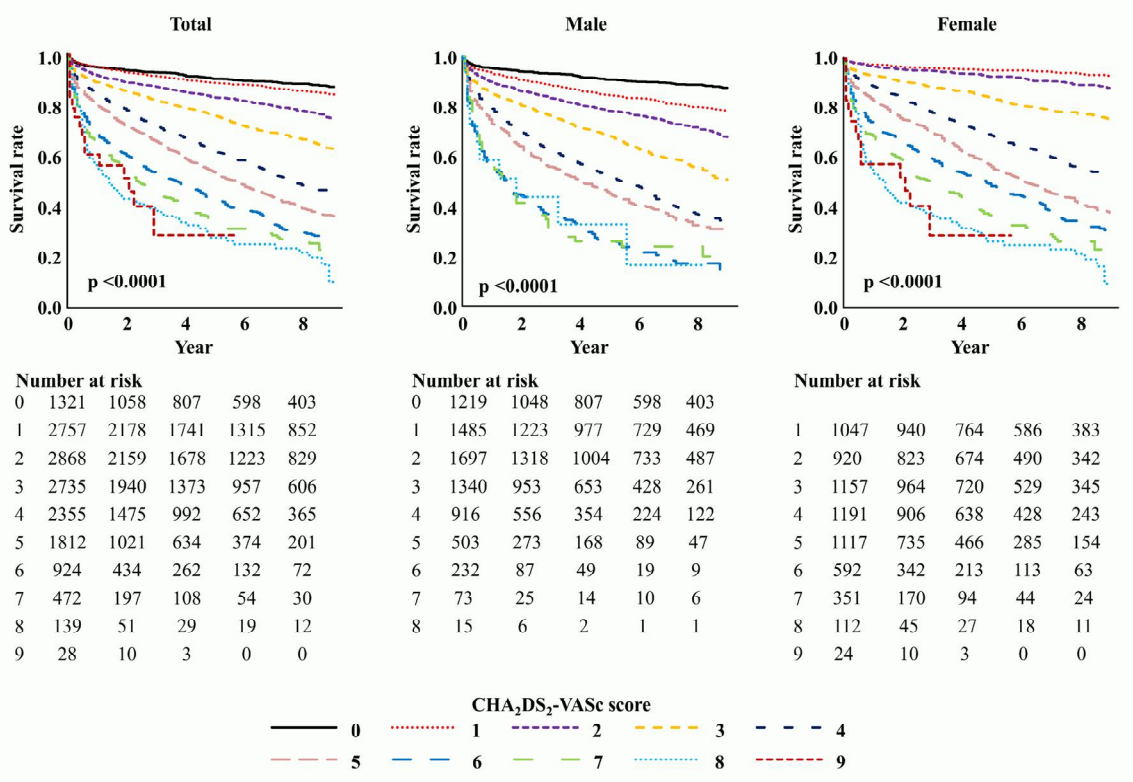

Figure 2. Kaplan-Meier survival curves according to CHA_2DS_2-VASc score. Survival rate was lower in atrial fibrillation patients with higher CHA_2DS_2-VASc score.

Cause of death in patients with atrial fibrillation

The causes of death observed in patients with AF differed from those in the entire NHIS-NSC cohort (Table 4). In patients with AF, diseases of the circulatory system (38.0%) constituted the most common cause of death, followed by malignant neoplasms (23.4%), and diseases of the respiratory system (8.4%). The most common cause of death in the entire cohort was malignant neoplasms (27.6%), followed by diseases of the circulatory system (22.4%) and injury, poisoning and other consequences of external causes (12.1%) (Table 4 and Figure 3).

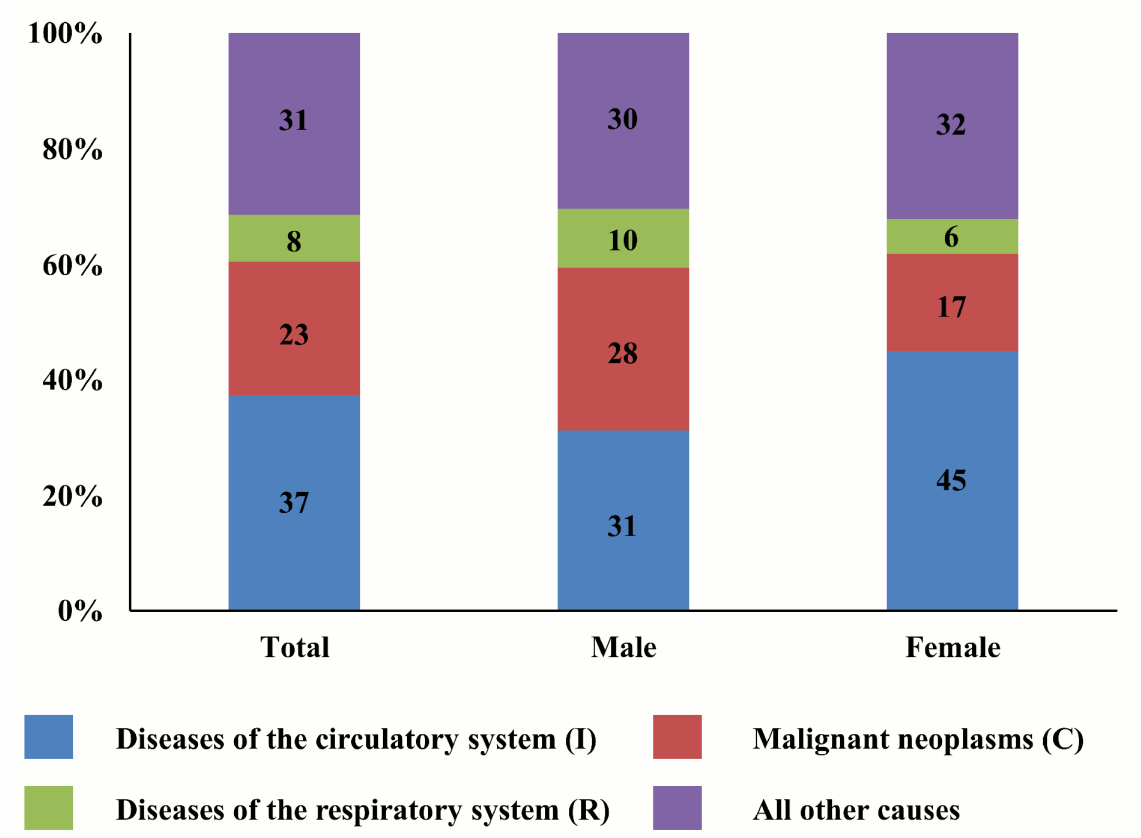

Figure 3. Proportion of specific causes of death in patients with atrial fibrillation according to ICD-10 codes. Bar graphs showed causes of death in overall AF patient, men, and women.

Table 4. Major causes of death in entire cohort and in patients with atrial fibrillation according to ICD-10 codes.

Rank	Total Cohort		AF patients	
	ICD-10 codes	Number (%)	ICD-10 codes	Number (%)
1	Malignant neoplasms (C)	15,440 (27.6)	Diseases of the circulatory system (I)	1,701 (38.0)
2	Diseases of the circulatory system (I)	12,546 (22.4)	Malignant neoplasms (C)	1,046 (23.4)
3	Injury, poisoning and certain other consequences of external causes (S & T)	6,779 (12.1)	Diseases of the respiratory system (J)	372 (8.4)
4	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R)	5,978 (10.7)	Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified (R)	275 (6.2)
5	Diseases of the respiratory system (J)	3,669 (6.6)	Endocrine, nutritional and metabolic diseases (E)	253 (5.7)
6	Endocrine, nutritional and metabolic diseases (E)	2,649 (4.7)	Injury, poisoning and certain other consequences of external causes (S & T)	195 (4.4)
7	Diseases of the digestive system (K)	2,496 (4.5)	Diseases of the digestive system (K)	156 (3.5)
8	Certain infectious and parasitic diseases (A & B)	1,332 (2.3)	Diseases of the genitourinary system (N)	124 (2.8)
9	Diseases of the nervous system (G)	1,303 (2.3)	Certain infectious and parasitic diseases (A & B)	108 (2.4)
10	Mental, behavioral and neurodevelopmental disorders (F)	1,025 (1.8)	Diseases of the nervous system (G)	71 (1.6)

AF, atrial fibrillation; ICD, international statistical classification of diseases and related health problems.

With regard to specific disease entities, cerebral infarction (I63, 7.8%) was the most common cause of death in patients with AF, followed by lung cancer (C34, 6.0%), myocardial infarction (I21, 5.0%), senility (R54, 4.5%), and sequelae of cerebrovascular diseases (I69, 4.5%). Causes of death differed between women and men. Cerebral infarction (I63, 9.5%) was the most common cause of death in women with AF, followed by senility (R54, 6.6%), sequelae of cerebrovascular disease (I69, 5.3%), acute myocardial infarction (I21, 5.1%) and heart failure (I50, 4.2%), whereas lung cancer (C34, 8.9%) was the most common cause among men with AF, followed by cerebral infarction (I63, 6.3%), acute myocardial infarction (I21, 4.8%), malignant neoplasms of the liver and intrahepatic bile ducts (C22, 4.1%), and chronic obstructive pulmonary disease (J44, 3.7%) (Table 5). In patients with AF aged <60 years, malignant neoplasms constituted the most common cause of death followed by cardiovascular diseases. However, this pattern was reversed in those aged ≥60 years (Figure 4).

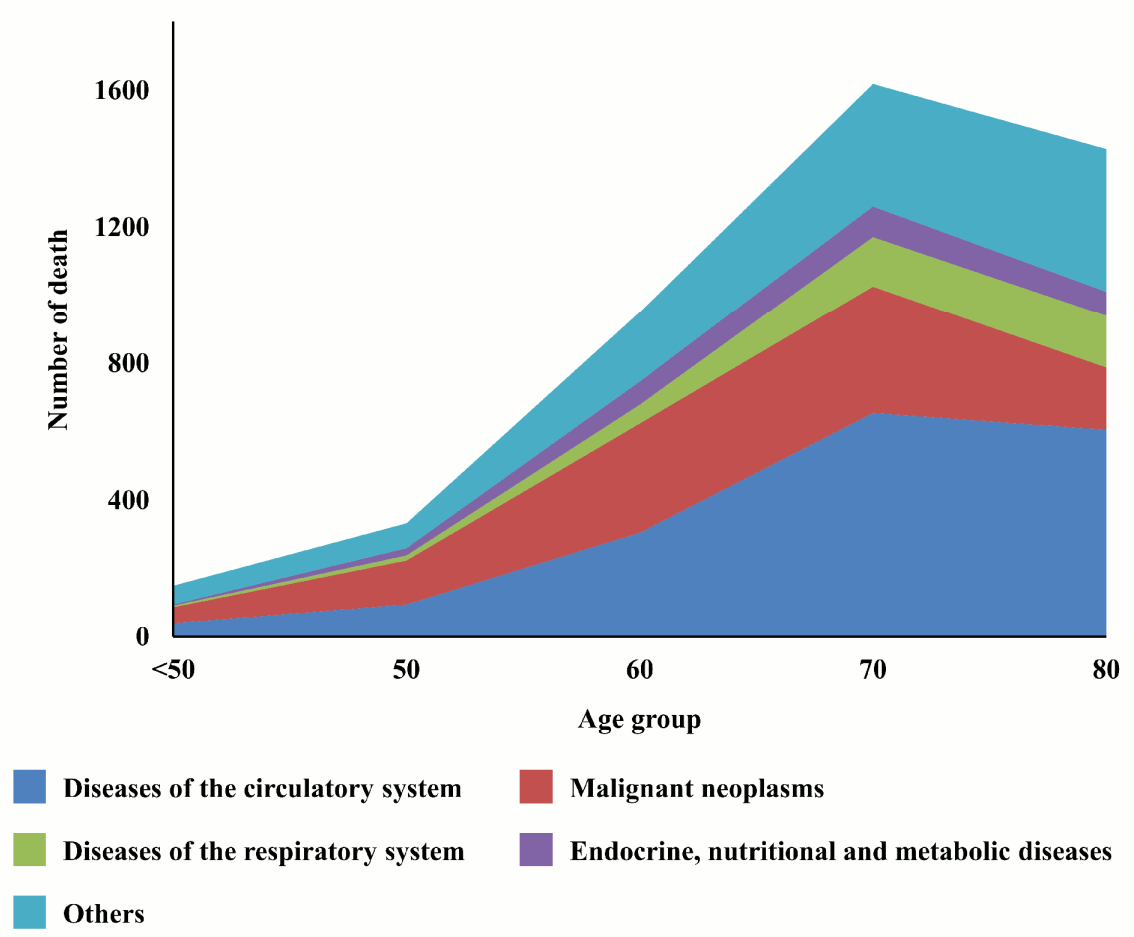

Figure 4. Cause of death in atrial fibrillation patients according to age group. Number of death was abruptly increased after age of 60. Malignant neoplasms and diseases of the circulatory system were the two most common causes of death in all groups. After age of 60, Number of death due to diseases of the circulatory system exceeds the number of death due to malignancy.

Table 5. Major specific causes of death in patients with atrial fibrillation according to sex (ICD-10 code).

	Total		Men		Women	
Rank	**Cause of death**	**N (%)**	**Cause of death**	**N (%)**	**Cause of death**	**N (%)**
1	Cerebral infarction (I63)	345 (7.8)	Malignant neoplasm of bronchus and lung (C34)	216 (8.9)	Cerebral infarction (I63)	194 (9.5)
2	Malignant neoplasm of bronchus and lung (C34)	266 (6.0)	Cerebral infarction (I63)	152 (6.3)	Senility (R54)	135 (6.6)
3	Acute myocardial infarction (I21)	221 (5.0)	Acute myocardial infarction (I21)	117 (4.8)	Sequelae of cerebrovascular disease (I69)	109 (5.3)
4	Senility (R54)	200 (4.5)	Malignant neoplasm of liver and intrahepatic bile ducts (C22)	99 (4.1)	Acute myocardial infarction (I21)	104 (5.1)
5	Sequelae of cerebrovascular disease (I69)	198 (4.5)	Chronic obstructive pulmonary disease (J44)	90 (3.7)	Heart failure (I50)	86 (4.2)
6	Type 2 diabetes mellitus (E11)	157 (3.6)	Gastric cancer (C16)	89 (3.7)	Type 2 diabetes mellitus (E11)	84 (4.1)

The cause-specific SMR indicated that patients with AF showed a higher risk of death from cardiovascular disease (SMR 5.69), malignancy (SMR 3.03), respiratory disease (SMR 5.30), and other causes (SMR 2.75) than that observed in the general population. The overall SMR and SMRs for cardiovascular diseases were higher in women with AF than in men with AF, whereas the SMRs for malignancy and respiratory disease were higher in men with AF than in women with AF (Table 6 and Fig 5).

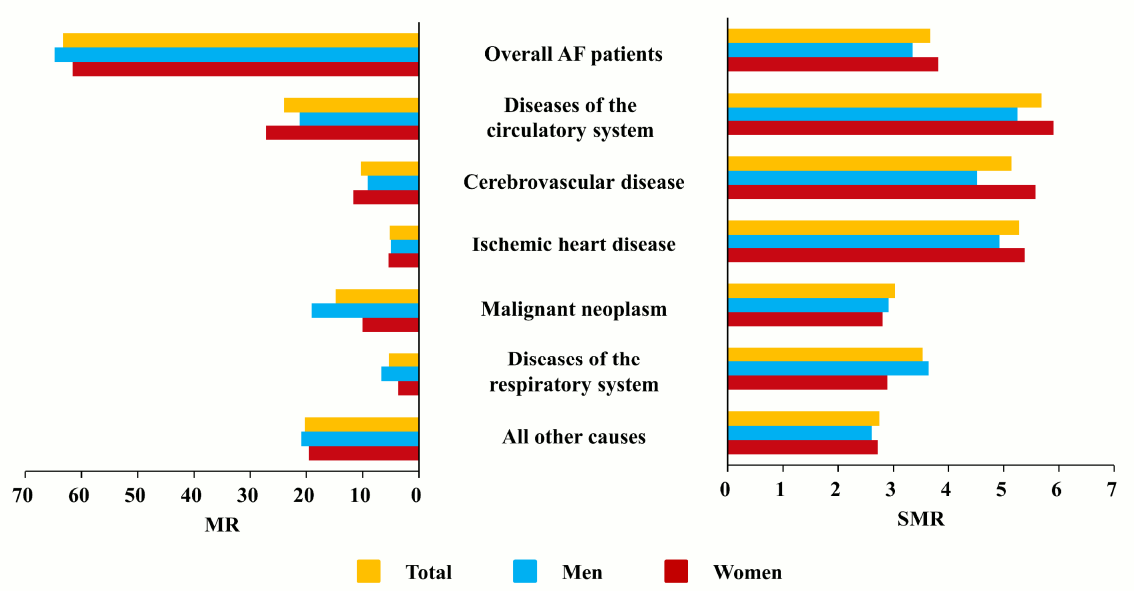

Figure 5. Mortality rates (MR) and standardized mortality ratios (SMR) of specific causes of death in atrial fibrillation patients according to ICD-10 codes. The overall mortality rate (MR) was higher in men than in women, but the MR due to diseases of the circulatory system was lower in men. The SMRs were generally higher in women than in men except for malignant neoplasms and diseases of the respiratory system.

Table 6. The cause-specific mortality rate and standardized mortality ratio in patients with atrial fibrillation according to ICD-10 code (the first code).

	Total			Men			Women		
	Death[a]	MR[b]	SMR (95% CI)	Death	MR	SMR (95% CI)	Death	MR	SMR (95% CI)
Diseases of the circulatory system (I)	1,701 (38.0)	24.0	5.69 (5.42-5.96)	796 (32.8)	21.2	5.25 (4.89-5.61)	905 (44.1)	27.2	5.91 (5.52-6.29)
Cerebrovascular diseases (I60-9)	732 (16.3)	10.3	5.14 (4.77-5.51)	341 (14.1)	9.1	4.51 (4.04-4.99)	391 (19.1)	11.7	5.57 (5.02-6.13)
Ischemic heart diseases (I20-5)	368 (8.2)	5.2	5.28 (4.74-5.82)	189 (7.8)	5.0	4.92 (4.22-5.62)	179 (8.7)	5.4	5.38 (4.59-6.17)
Hypertensive diseases (I10-3)	151 (3.4)	2.13	5.47 (4.59-6.34)	63 (2.6)	1.68	6.6 (4.97-8.23)	88 (4.3)	2.64	4.94 (3.91-5.97)
Heart failure (I50)	145 (3.2)	2.04	6.99 (5.85-8.13)	59 (2.4)	1.57	7.85 (5.85-9.86)	86 (4.2)	2.58	6.56 (5.17-7.94)
Other circulatory diseases	305 (6.8)	4.31	7.91 (7.02-8.79)	144 (5.9)	3.84	6.99 (5.85-8.13)	161 (7.8)	4.83	8.51 (7.2-9.83)
Malignant neoplasms (C)	1,046 (23.4)	14.8	3.03 (2.84-3.21)	714 (29.4)	19.1	2.91 (2.70-3.13)	332 (16.2)	10.0	2.81 (2.51-3.11)
Diseases of the respiratory system (J)	372 (8.4)	5.3	5.30 (3.53-3.17)	250 (10.3)	6.7	3.64 (3.28-4.09)	122 (6.0)	3.7	2.89 (2.38-3.40)
Other causes	1,434 (32.0)	20.3	2.75 (2.61-2.89)	782 (32.2)	20.9	2.61 (2.43-2.79)	652 (31.8)	19.6	2.72 (2.51-2.92)
Overall	4,479 (100)	63.3	3.67 (3.56-3.78)	2,427 (100)	64.8	3.35 (3.21-3.48)	2,052 (100)	61.6	3.81 (3.65-3.98)

[a]Death events were presented as number (percentage).; [b]MR was presented as the number of death per 1,000 person-year.

AF, atrial fibrillation; CI, confidence interval; ICD, international statistical classification of diseases and related health problems; MR, mortality rate; SMR, standardized mortality ratio

Mortality from specific diseases of the circulatory system in patients with atrial fibrillation

Cerebrovascular disease (I60-69) was the most common cause of death (732 patients, 43.0%) in those of deaths from diseases of the circulatory system (1,701 deaths). Of note, cerebral infarction (I63) was the most common specific disease accounting for 47.1% of cerebrovascular disease (Table 6). Ischemic heart disease (I20-25) was the second most common specific cause of death, followed by hypertensive diseases and heart failure. The cause-specific SMR showed that patients with AF demonstrated a higher risk of death related to cerebrovascular disease (SMR 5.14), ischemic heart disease (SMR 5.28), hypertensive diseases (SMR 5.47), and heart failure (SMR 6.99). Women with AF showed a higher mortality rate and SMR related to cerebrovascular disease and ischemic heart disease than that in men (Table 6).

Discussion

In this population-based study, we observed that patients with AF showed a 3.67-fold higher risk of all-cause death than that in an age- and sex-matched general population. Women with AF showed a higher SMR than men with AF, suggesting that the effect of AF on death was greater in women than in men. The leading cause of AF-associated deaths was diseases of the circulatory system, and cerebral infarction was the most common cause of death. Patients with AF showed a 5.5-fold higher risk of death from the diseases of the circulatory system than that in the general population.

In this current study, we observed that the crude mortality rate for all-cause death was 63.3 per 1,000 person-years, which was similar to the all-cause mortality rate of 60.5 per 1,000 person-years reported by the Framingham study [3]. A Japanese study reported a lower crude mortality rate of all-cause deaths as 21.7 per 1,000 person-years; however, the study included only a small number of patients with AF (n=60) [11]. We observed that patients with AF in Korea had a 3.7-fold higher risk of mortality than that observed in the general population, which is higher than that reported in Europe and US [5, 20-22]. In a Swedish study, the risk of mortality in the patients with AF was 1.6-fold higher than that in the general population [5]. A Serbian population-based observational study have shown that the risk of AF for all-cause mortality was 2.43-fold higher and for cardiovascular mortality was 3.03-fold higher than those in the Serbian population [20]. However, those studies included only a limited number of patients. In US, AF was associated with a 1.5- to 1.9-fold increased risk of death in both men and women [21], and similar result was reported in the other study [22]. We observed that patients with AF showed a higher risk of mortality than that in an age-matched general population. Age has been regarded as a strong risk factor for mortality and morbidity in patients

with AF, although other causes of death are also known to play an important role in older individuals [23]. A higher prevalence of permanent or persistent AF and a higher CHA_2DS_2-VASc score may contribute to unfavorable outcomes in old age [24]. Therefore, the mortality risk in older patients with AF is higher than that in younger patients with AF. However, the impact of AF on mortality differs with age. The absolute mortality (number of deaths) was lower in younger patients with AF; however, the impact of AF on mortality was higher than that in older patients. In contrast, the absolute mortality was higher in older patients with AF, although the SMR was observed to be lower than that in younger patients with AF, which suggests that the impact of AF on mortality weakens with aging. As individuals without AF become older, they show the development of concomitant comorbidities other than AF, which could contribute to an increased risk of mortality, thereby weakening the impact of AF in older patients with AF. A possible explanation for this observation could be the multifactorial etiologies of AF noted in younger patients. Congenital heart diseases are known to be an important etiological contributor in young patients with AF, which could also affect survival [25]. Familial AF, which develops at a relatively young age, shows a strong relationship with genetic mutations and might affect the long-term prognosis [26]. An excessive lifestyle, heavy consumption of alcohol, and endurance exercise all tend to predispose individuals to the development of AF compared to the risk in the general population, which could affect survival [27, 28]. To our knowledge, this is the first population-based study comprising an adequate number of patients (n=2,604, aged <50 years) that has reported an increased impact of AF on mortality particularly in young patients.

Female sex is an important risk factor for stroke in patients with AF, which, therefore, has been incorporated in the CHA_2DS_2-VASc score [23]. The effect of sex on the survival of patients with AF remains controversial. AF is shown to be a stronger risk factor for stroke and cardiovascular death in women than in men [7, 22]. This tendency has also been observed in patients at a low risk [29]. However, a German study has demonstrated a similar/comparable risk of stroke between women and men with AF [30]. Renoux et al. reported that case-fatality was higher in men than in women [31]. Two studies comprising Asians have also shown similar results [10, 32]. The Framingham study showed a difference in the prognostic significance of sex on mortality in patients with AF [3]. The odd ratios for death in women and men with AF compared with non-AF controls were 1.9 and 1.5, respectively [3]. A recent meta-analysis reported that AF is a stronger risk factor for cardiovascular disease and death in women than that in men [4]. Additionally, a study from Taiwan reported that women with AF with a CHA_2DS_2-VASc score of 1 demonstrated a higher risk of ischemic stroke than that observed in non-AF patients, whereas no such association was observed in men with AF [29]. In our study, we noted that women showed a higher SMR than men across all age groups. Furthermore, women with AF demonstrated a higher mortality rate and SMR with regard to cerebrovascular disease and ischemic heart disease than that in men. The increased risk of mortality in women is attributable to several factors—although women demonstrate a higher risk of stroke, they are less likely to be prescribed oral anticoagulants than men [33]. Recently, a nationwide population-based study reported that women were more likely to be undertreated with oral anticoagulants than men [34]. Furthermore, women showed a higher risk of bleeding events with oral anticoagulant use [35].

We observed that cardiovascular disease was the leading cause of death in patients with AF and that these patients were at a 5.7-fold higher mortality risk due to cardiovascular disease than that observed in the general population. Our results were in agreement with previous studies showing that cardiovascular disease was the leading cause of death in patients with AF [22, 31, 36-39]. A cohort study based on a registry of patients with AF across 47 countries revealed that heart failure was the most common cause of death, followed by stroke [9]. Another study revealed that ischemic heart disease was the most common underlying cause of death among decedents with AF [8]. A Swedish study also showed that ischemic heart disease and myocardial infarction were more common causes of death than cerebral infarction or bleeding [5]. In contrast to Western studies, we observed that cerebral infarction was the most common specific cause of cardiovascular death. Among Asians, cerebral infarction was a more common cause of death than ischemic heart disease [40-42]. East Asian countries have shown a higher stroke and lower coronary heart disease mortality [41]. Another large Chinese cohort study has also shown that age-adjusted stroke mortality was 3-fold higher than coronary heart disease mortality [42]. Moreover, a comparative study between Asian-Americans and non-Hispanic whites showed higher cerebrovascular disease-related mortality in the former group, whereas heart failure- and ischemic heart disease-related mortality rates were higher in the latter [43]. A possible explanation for this racial difference in the cause of death is that the slope of the relationship between blood pressure and stroke was noted to be steeper in Asians [44]. Another possible explanation is that oral anticoagulants is underutilized in Asia compared to Western countries. The GARFIELD-AF registry showed that the use of oral anticoagulation therapy was lower in Asia than that in other region [45]. In GLORIA-AF phase I study, the proportion of

use of vitamin K antagonists (VKA) is 20.3% in Chinese patients with AF. It is similar to this study but is much lower than Europe (64%) and Middle East (45%) [46]. Underutilization of oral anticoagulants were associated with an increased risk of stroke that were generally higher in Asian than in non-Asians [47].

There are some limitations in this study. First, definitions of AF and other comorbidities were based on the NHIS claim data, and the causes of death were based on ICD-10 diagnosis codes. Thus, the possibility of under- or overestimation of the number of patients with AF and the cause of death cannot be ignored. However, we used the same definition and validated it in our previous studies [2, 48]. Second, although it would be reasonable to adjust several clinical variables with could affect the survival, the Korean mortality database provided by Statistics Korea, a government agency, did not contain these information. In addition, detailed information regarding the type of AF could not be verified in this claims data. Third, this study included only Koreans; thus, our results may not be generalizable to other populations. Nevertheless, this is the largest study that included patients with AF across all age groups using a nationwide population-based cohort. It allowed comprehensive analysis of mortality and the assessment of detailed mortality patterns in patients with AF.

Conclusion

In this nationwide population based study, patients with AF showed a 4-fold higher risk of mortality than that observed in the general population. Although the absolute mortality rate was higher in older patients and men, the prognostic impact of AF was greater in younger patients and women. Diseases of the circulatory system were

observed to be the leading cause of death. Notably, cerebral infarction was the most common specific disease associated with mortality, in contrast to findings observed in the Western population. It is important to characterize mortality patterns to establish more effective treatment strategies in patients with AF. Therefore, optimal management of cardiovascular risk factors and close attention to prevention of cerebral infarction are warranted to reduce mortality in Asians with AF.

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요약 (국문초록)

서론: 심방세동 환자들은 단순히 일반 인구 집단에 비해서 사망률이 높다고 알려져 있다. 그러나 나이, 성별에 따라 심방세동이 사망률에 미치는 영향이 어떠한지, 그리고 구체적인 사망의 원인이 무엇인지에 대한 대규모 연구가 거의 없는 실정이다.

방법: 국민건강보험공단 표본 코호트에서 추출한 15,411 명의 심방세동 환자들의 사망 원인을 ICD-10 분류 체계로 확인하였다.

결과: 2002 년부터 2013 년까지 총 4,479 명 (29%)이 사망하였다. 조사망률은 1 천 인년 당 63.3 이었다. 심방세동 환자들은 일반 인구 집단에 비해서 3.7 배의 사망 위험을 나타내었다. 표준화 사망비는 젊은 환자에서 가장 높았고 나이가 들수록 점자 감소하였다 (20 세 미만의 표준화 사망비 21.93, 95% 신뢰구간 7.60-26.26; 80 세 이상의 표준화 사망비 2.77, 95% 신뢰구간 2.63-2.91). 여성 심방세동 환자의 사망 위험이 남성 심방세동 환자의 사망 위험보다 높았다 (여성의 표준화 사망비 3.81, 95% 신뢰구간 3.65-3.98; 남성의 표준화 사망비 3.35, 95% 신뢰구간 3.21-3.48). 심방세동 환자들의 가장 흔한 사망 원인은 심혈관계질환이었고 (38.5%), 뇌경색이 그 중에서도 가장 흔한 원인이었다. 심방세동 환자들이 심혈관계 질환으로 사망할 위험은 일반 인구 집단에 비해서 5 배 가량 높았다.

결론: 심방세동 환자들은 일반 인구 집단에 비해서 4 배 가량 사망 위험이 높았다. 그러나 심방세동이 사망에 미치는 영향은 나이가 들수록 감소하였고, 남성에서 약화되었다. 뇌경색은 심방세동 환자의 가장 흔한 사망 원인으로, 뇌경색의 위험을 줄이려는 추가적인 노력이 필요하겠다.

주요어: 심방세동; 사망률; 표준화 사망비; 사망 원인; 인구집단연구; 역학;

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