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Association between atrial fibrillation and the risk of glaucoma development: a 12-year Nationwide cohort study

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OBJECTIVE: To investigate the risk of glaucoma development in patients with atrial fibrillation (A-fib) using Korean National Health Insurance Service data.

METHODS: The present study used a National Sample Cohort consisting of approximately one million random subjects who were tracked from 2002 to 2013 (12 years). Newly diagnosed glaucoma and A-fib were included based on the Korean Classification of Disease codes. The A-fib group consisted of patients who received an initial A-fib diagnosis between January 2003 and December 2007 as an index period ($n = 8765$). The control group ($n = 43{,}352$) was selected using a 1:5 propensity-score matching for social and demographic factors. Each subject was followed up until 2013. Multivariate Cox proportional hazard regression analysis was performed to compare the risk of glaucoma development between the A-fib group and the control group.

RESULTS: The rate of glaucoma development was 3.54% in the A-fib group and 2.96% in the control group ($P < 0.0001$). A-fib increased the risk of glaucoma development [hazard ratio = 1.31; 95% confidence interval (CI): 1.15 to 1.48] after adjusting for age, sex, comorbidities, residence, household income, and year of enrollment. In multivariable Cox regression analysis, patients with comorbidity of diabetes mellitus and chronic renal failure and those aged ≥50 years showed significantly higher risk of glaucoma development (all $P < 0.001$).

CONCLUSIONS: A-fib was significantly associated with the development of glaucoma after adjusting for potential confounding factors. Physicians may need to monitor patients with A-fib carefully for possible glaucoma development.

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INTRODUCTION

Glaucoma is an important public-health issue and one of the leading causes of irreversible blindness worldwide [1]. Glaucoma is a progressive optic neuropathy followed by a defect of the retinal-nerve fiber layer (RNFL), which is accompanied by corresponding visual field defects [2]. Glaucoma is recognized as a multifactorial optic neuropathy. It remains as a disease with an unclear etiology. Increased intraocular pressure (IOP) is a major risk factor of glaucoma. However, other risk factors such as vascular injury and hypoxia might be also related to the pathogenesis of glaucoma [3–5]. A repeated reperfusion injury (for example, IOP fluctuation or disturbed autoregulation) could also bring about oxidative stress and lead to glaucomatous damage in the long run even if the injury is mild [6]. Cardiovascular disorders (including vasospasm, hypertension, and hypotension) and diabetes are possible risk factors for glaucoma [7–14].

Similar to glaucoma, atrial fibrillation (A-fib) is a disorder of significant importance in public health. A-fib is one of the most common cardiac arrhythmias. A-fib presents an utterly irregular heart rate that can lead to unstable ocular perfusion pressure and eventually result in an unstable ocular blood flow. Flammer et al. have described that unstable ocular perfusion may lead to ischemia and reperfusion damage, which may contribute to the vascular theory of pathogenesis of glaucoma [15]. The number of people with A-fib in the world was estimated to be more than 33 million in 2010 [16]. A-fib is considered to be a major cause of cardiovascular morbidity, heart failure, stroke, and sudden death.

Patients with A-fib already have systemic disorders and many A-fib patients have comorbidity of hypertension or diabetes. Additional vision-threatening diseases such as glaucoma could worsen patients' quality of life, for example, contributing to difficulties in near and distant activities and driving [17, 18]. Even with good visual acuity, moderate visual field defects more influenced the quality of life of glaucoma patients [17, 18]. Since cardiovascular disease and glaucoma are both chronic diseases, if a patient has both disorders, medical burden might be aggravated during the lifetime [19].

Several studies using Korean National Health Insurance Service data have reported that the risk of glaucoma is higher in those with diabetes and hypertension (well-known cardiovascular risk factors) than in those without them [20–22]. However, the

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association between cardiovascular disease, especially A-fib, and the risk of glaucoma development using Korean National Health Insurance Service data has not been reported yet.

To the best of our knowledge, the association between A-fib and glaucoma has not been investigated in a longitudinal study with a large sample before, especially in a single ethnic group of Asians (Koreans). Thus, the objective of this study was to investigate the risk of subsequent glaucoma development after A-fib diagnosis using a representative sample of nationwide one million subjects of the National Health Insurance Service -National Sample Cohort from 2002–2013 dataset in South Korea.

MATERIALS AND METHODS

Data sources

This retrospective cohort study used a random sample of 1,025,340 subjects from the National Health Insurance Service-National Sample Cohort 2002–2013 dataset. The sample accounted for approximately 2.2% of the whole population of Korea in National Health Insurance Service of 2002. Data were extracted from the National Health Insurance Service using systematic random sampling for research purposes. Korea has retained a nationwide health-insurance system since 1963 under the Korean National Health Insurance Service. Almost all data in the health insurance system are integrated in a large data source. Health Insurance claims data include diagnostic and, procedure codes, prescription of medicines, personal information, and medical care costs. Moreover, the Korean National Health Insurance Service employs the Korean Classification of Diseases (KCD), which resembles the International Classification of Diseases (ICD). Data resource profile regarding the National Health Information Database of the National Health Insurance Service in South Korea has been previously described in detail [23].

Study population

Inclusion criteria were: (1) patients in the study cohort who received medical care between January 1st, 2003 and December 31st, 2007 with a newly diagnosed A-fib (KCD code I48, corresponding to ICD-9-CM code 427.3, A-fib and flutter, case cohort group); (2) subjects (comparison control cohort) drawn using a 1:5 propensity-score matching from the dataset of 1 million participants without A-fib between January 2003 and December 2007; (3) patients newly diagnosed as having glaucoma (ICD-10 codes H40.1: primary open-angle glaucoma, H40.2: primary angle-closure glaucoma, H40.3, H40.4, H40.5, H40.6: other types of glaucoma) who received eyedrop medication (prescribed at ophthalmology) after the diagnosis of A-fib from 2003 to 2013 to calculate glaucoma occurrence as the main outcome. Newly diagnosed glaucoma patients did not receive eyedrop medication before the diagnosis of glaucoma. Exclusion Criteria were: (1) patients with pre-existing A-fib before 2003; (2) patients with glaucoma occurring before the development of A-fib, depending on the date of visit. Those patients with acute myocardial infarction (KCD code I21 corresponding to ICD-9-CM code 410, AMI) was not included in the present study.

Matching was done with the following variables: (1) age (<50/50–59/60–69/70–79/≥ 80 years), (2) sex, (3) household income (≤30%, 30–70%, and ≥70%), (4) year of enrollment (2003–2007), and (5) residential area. Inclusion and exclusion of subjects and propensity matching were performed according to previously reported methods [20–22, 24]. The ≤ 30% household income means the lower income participant who pays the health insurance premium which is the 0th to 3rd deciles. The 30–70% are the health insurance premium which is the 4th to 7th decile. And the ≥ 70% are the health insurance premium which is the 8th to 10th decile. A diagram of the study design regarding the extraction and follow-up of subjects is shown in Fig. 1a. A flowchart regarding inclusion and exclusion, and follow up loss (death) has been demonstrated as Fig. 1b.

Comorbidities

Hypertension was defined on the basis of KCD code I10 (corresponding to ICD-9-CM code 401, essential hypertension), diabetes mellitus with KCD code E10–E14 (corresponding to ICD–9–CM code 250, Diabetes mellitus), chronic renal failure with KCD code N18 (corresponding to ICD-9-CM code 585, Chronic kidney disease), and hyperlipidaemia with KCD code E78.0–78.5 (corresponding to ICD–9–CM codes 272.0, pure hypercholesterolemia; 272.1, pure hyperglyceridaemia; 272.2, mixed hyperlipidaemia; 272.3, hyperchylomicronaemia; and 272.4, other and unspecified hyperlipidaemia) as comorbidities. These comorbidities had to be diagnosed between 2003 and 2013 and prior to the A-fib diagnosis in the case-cohort group of matched pairs.

Statistical analysis

Propensity-score matching was carried out to estimate the occurrence of A-fib. Propensity scores were calculated employing logistic regression to control socio-demographic factors, including gender, age, household income, and residential area. Residential area was categorized into four areas including: (1) the 1st area, metropolitan area of Seoul; (2) the 2nd area, the largest province; (3) the 3rd area, the second-largest city and the 2nd and 3rd largest provinces; and (4) other areas included in the 2nd or the 3rd area. Matching was carried out using the Greedy $8 \rightarrow 1$ digit-matching macro along with the calculated propensity score of each year from 2003 to 2007.

To calculate the hazard associated with A-fib, hazard ratios (HRs) and 95% confidence intervals (CIs) were analyzed with univariate and multivariate Cox proportional hazard regression methods. In the multivariate analysis, we used four models to determine the risk of glaucoma development in CRD. In model 1, only two confounding factors (age groups and sex) were selected. In model 2, confounding factors that were significant in univariate analysis were selected. In model 3, confounding factors were selected with the best subset selection method, a method that could find the lowest Akaike information criterion (AIC) value among all possible combinations of independent variables. Model 4 was a model that included all independent variables.

We used the Kaplan–Meier curve to analyze cumulative incidence of glaucoma in each year with 11 years of follow-up period (2003–2013). If a patient died during the study period who did not develop glaucoma or return to the hospital until the end of the study, the patient was regarded as censored. Follow-up started from the first date of A-fib diagnosis. For the comparison control group, it started at a randomly selected index date during the matched year. Follow-up finished at the last visit date up to 2013 for subjects without subsequent glaucoma or the first date of glaucoma diagnosis (Fig. 1a).

To test differences in proportions for glaucoma event, demographic factors, and other variables between the control group and the A-fib group, Pearson's Chi-square test was performed. Statistical significance was acknowledged at $P < 0.05$. SAS System version 9.4 (SAS Institute, Inc., Cary, NC, USA) and Stata/MP version 14.0 (StataCorp, College Station, TX, USA) were used for all statistical analyses.

RESULTS

Baseline characteristics

A total of 52,117 subjects (43,352 controls without A-fib and 8765 patients with A-fib) were eligible for the final analysis. Throughout the whole follow-up period (median, 7.7 years, min-max; 7–4017 days), glaucoma developed more frequently in subjects with A-fib than in those without A-fib (3.54% vs. 2.96%, $P < 0.0042$). Comorbidities such as diabetes mellitus, hypertension, chronic renal failure, and hyperlipidemia were more common in the A-fib group than in the socio-demographic-matched control group ($P < 0.0001$ for all). There was no significant difference in the proportion of patients according to the presence of A-fib for socio-demographic variables used for matching between the two groups (Table 1).

Factors associated with glaucoma incidence

Univariate Cox proportional hazard regression results are shown in Table 2. Four multivariate models were built, including the one with all variables adjusted (model 4). We found that glaucoma was associated with a following diagnosis of A-fib (hazard ratio [HR]: 1.31; 95% confidence interval [CI]: 1.15–1.48) in model 4 and in the other 3 models (HR = 1.4 in model 1, HR = 1.3 in model 2, and HR = 1.32 in model 3). Comorbidity of diabetes mellitus (HR: 1.3; 95% CI: 1.15–1.47) and chronic renal disease (HR: 1.97; 95% CI: 1.35–2.89) were significantly associated with glaucoma development in our multivariate model 4. They were also significant in model 2 and in model 3 (all $P < 0.001$, Table 3). However, other comorbidities such as hypertension and hyperlipidemia failed to

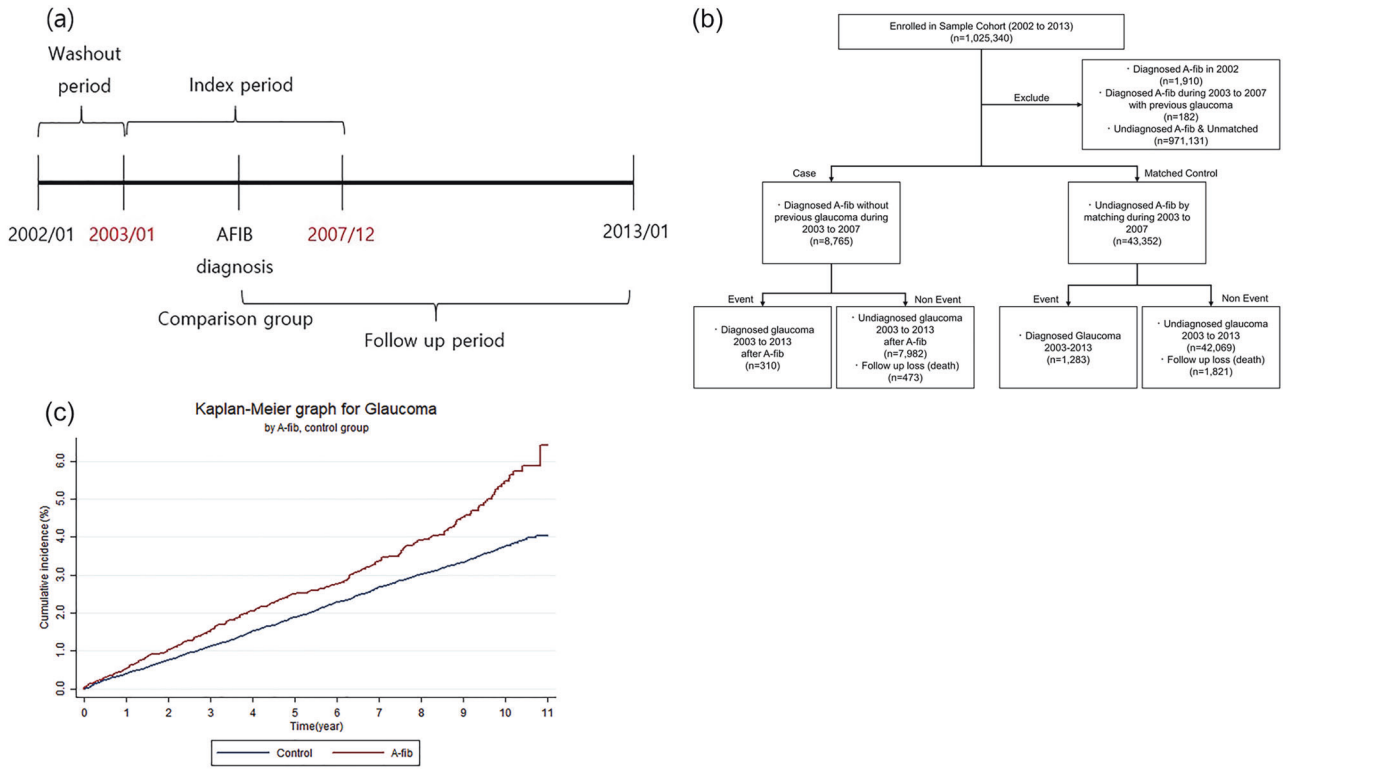

Fig. 1 Diagram of the longitudinal cohort study. a Study design of a nationwide cohort of one million for 12 years. There was a one-year washout period between January 1st, 2002 and December 31st, 2002. The index period was between January 1st, 2003 and December 31st, 2007. Newly diagnosed A-fib (KCD code I48) was defined as the A-fib cohort group. Subjects (comparison control cohort) were extracted using a 1:5 propensity-score matching from the database of 1 million subjects without A-fib between January 2003 and December 2007. Patients newly diagnosed as having glaucoma (ICD-10 code H40., glaucoma) who received eyedrop medication (prescribed at ophthalmology) after the diagnosis of A-fib were followed up from 2003 until 2013 (follow-up period) to assess glaucoma occurrence as the outcome variable. Newly diagnosed glaucoma patients did not receive eyedrops before the diagnosis of glaucoma. **b** Flowchart of the study. A flowchart regarding inclusion and exclusion, and follow up loss (death) throughout the whole follow up period has been demonstrated. Newly diagnosed atrial fibrillation (case) and matched control and the development of newly diagnosed glaucoma (event) after the diagnosis of atrial fibrillation (case) have been shown in this flowchart. **c** Cumulative incidence of glaucoma for up to 11 years by Kaplan–Meier survival curves. Those with A-fib had higher incidence of glaucoma than the control group without A-fib. Kaplan–Meier survival curves for the A-fib group and control group showed significant differences using the log-rank test ($P < 0.0001$). Cumulative incidence of glaucoma at 11 years was significantly higher in the A-fib group (6.42%) than in the control group without A-fib (4.02%). Cumulative incidence of glaucoma in the A-fib group was higher than that in the control group at each time point during the follow-up period of 11 years.

show significant associations with glaucoma development in model 4, model 2, or model 3 (all $P > 0.05$).

The age group of more than 50 years showed significantly higher incidence of glaucoma than the age group of less than 50 years as the reference group ($P < 0.010$). The adjusted HR was 2.78 (2.28–3.39) for age of 50–59 years, 4.05 (3.37–4.86) for age of 60–69 years, 4.63 (3.83–5.61) for age of 70–79 years, and 2.91 (2.25–3.78) for age of more than 80 years in model 4. All other models consistently showed the same tendency (all $P < 0.001$). Men and women did not show significant difference in the incidence of glaucoma in our calculated study subjects in model 4 ($P = 0.405$) or model 1 (Table 3).

We analyzed residential areas with metropolitan Seoul as reference. The second and third areas did not show any significant difference in the development of glaucoma in model 2, 3, or 4 (all $P > 0.121$). However, the fourth area showed significantly less development of glaucoma in models 2, 3, and 4 (all $P < 0.001$), with HR of 0.82 in model 4. Household income showed no significant difference among 0–30%, 30–70%, and 70–100% in model 4 (all $P > 0.445$) (Table 3).

Cumulative incidence for glaucoma

Kaplan–Meier curves for cumulative incidence of glaucoma in each year for up to 11 years are shown in Fig. 1c. Those with A-fib had glaucoma more frequently than those without A-fib in the control group. Kaplan–Meier curves for the A-fib group and the control group showed a significant difference using the log-rank test ($P < 0.0001$). Cumulative incidence of glaucoma at 11 years was significantly higher in the A-fib group (6.42%) than in the control group without A-fib (4.02%). Cumulative incidence of glaucoma at each time point of each year during the 11 years of follow-up is shown in Table 4. Cumulative incidence of glaucoma was 1.55% in the A-fib group and 1.12% in the control group at three years. At 5 years, it was 2.49% in the A-fib group and 1.88% in the control group. At seven years, it was 3.36% in the A-fib group and 2.68% in the control group. At 10 years, it was 5.47% in the A-fib group and 3.76% in the control group. Cumulative incidence of glaucoma in the A-fib group was higher than that in the control group at each time point during the follow-up period of 11 years (Table 4).

DISCUSSION

To the best of our knowledge, this is the first study to demonstrate the significant association between newly diagnosed A-fib and subsequent glaucoma development using a cohort of one million subjects with long-term follow-up of 12 years based on the Korean National Health Insurance Service dataset. Since A-fib is the most

Table 1. Characteristics of the study population.

Variables	Control (*N* = 43,352)	A-fib (*N* = 8765)	*P* value
Glaucoma			0.0042
No event	42,069 (97.04)	8455 (96.46)	
Event	12,83 (2.96)	310 (3.54)	
Hypertension			<0.0001
No	31,500 (72.66)	4415 (50.37)	
Yes	11,852 (27.34)	4350 (49.63)	
Diabetes mellitus			<0.0001
No	36,047 (85.18)	6274 (71.58)	
Yes	7305 (16.85)	2491 (28.42)	
Chronic renal failure			<0.0001
No	43,102 (99.42)	8594 (98.05)	
Yes	250 (0.58)	171 (1.95)	
Hyperlipidaemia			<0.0001
No	37,208 (85.83)	6435 (73.42)	
Yes	6144 (14.17)	2330 (26.58)	
Variables for matching			
Year			0.7247
2003	9397 (83.19)	1899 (16.81)	
2004	8830 (82.79)	1836 (17.21)	
2005	9258 (83.51)	1828 (16.49)	
2006	7972 (83.22)	1608 (16.78)	
2007	7895 (83.2)	1594 (16.8)	
Age group (year)			0.8309
<50	11,865 (83.33)	2374 (16.67)	
50–59	7705 (83.3)	1545 (16.7)	
60–69	10,930 (83.23)	2203 (16.77)	
70–79	8733 (83.09)	1777 (16.91)	
≥80	4119 (82.63)	866 (17.37)	
Sex			0.8849
Male	22,260 (83.16)	4508 (16.84)	
Female	21,092 (83.21)	4257 (16.79)	
Residence			0.9999
Seoul (metropolitan)	8388 (83.19)	1695 (16.81)	
2nd area	2366 (83.13)	480 (16.87)	
3rd area	2949 (83.19)	596 (16.81)	
4th area	29,649 (83.18)	5994 (16.82)	
Household income			0.9906
0–30%	9275 (83.14)	1881 (16.86)	
30–70%	14,794 (83.2)	2988 (16.8)	
70–100%	19,283 (83.19)	3896 (16.81)	

A-fib atrial fibrillation.
P-value by Chi-square test.
Percent proportion is indicated in ().

common cardiac arrhythmia and glaucoma is one of the leading causes of irreversible visual loss, both A-fib and glaucoma are of significant social importance in terms of public-health care. We found that subsequent glaucoma developed significantly more frequently in subjects with newly diagnosed A-fib than in those without A-fib. Cumulative incidence of glaucoma was significantly higher in subjects with A-fib than in those without A-fib at 11 years of follow-up.

In the sequence of A-fib, conditions prone to the formation of intracardiac thrombus may cause macro- and microembolisms [25]. Microembolic complications may go unnoticed in clinical ophthalmologic practice [26, 27]. However, repeated microemboli occlusion of any level of ophthalmic artery or branched posterior ciliary artery or central retinal artery and subsequent reperfusion causes reperfusion injury, which could lead to unstable ocular perfusion of either choroid or retina [28]. Repeated transient ischemic episodes may bring about perfusion disturbance and RGC death, which can lead to glaucomatous change [28].

A-fib as the most common cardiac arrhythmia may lead to unstable ocular perfusion. Unstable ocular perfusion is represented by PVD such as migraines and orthostatic hypotension, which is a considerable risk factor of glaucoma [15, 29, 30]. Numerous population-based studies have demonstrated that a decreased diastolic ocular perfusion pressure is one of risk factors of glaucoma [31–33]. Besides this factor, nocturnal hypotension, low BP, orthostatic hypotension, unstable mean ocular perfusion pressure, autonomic dysfunction, peripheral microcirculation abnormality, and PVD are also features of glaucoma patients [34–39]. These mechanisms of A-fib might have influenced the following development of glaucoma in A-fib patients in our study.

Some studies have indicated a possible association between A-fib and glaucoma. However, none of them was a population-based study with a big data setting. Earlier studies have reported that cardiac arrhythmias, especially A-fib, were related with impairment of visual acuity and visual field defects in elderly glaucoma patients [40]. Glaucoma patients had significantly more A-fib than the control group in this previous study [40]. The same author group in Finland found that A-fib and low systolic blood pressure were associated with impairment of ocular functions in elderly glaucoma patients [41]. However, they were institutionalized elderly glaucoma patients and may not represent general population. The diagnostic criteria were not clear from these old papers, but possibly most of them were primary open-angle glaucoma (POAG) with high IOP. Another hospital-based study of Polish patients reported that A-fib, independent of well-known other cardiovascular factors, increased the risk of developing normal-tension glaucoma [28]. Although these studies were hospital-based studies, they all reported the association between A-fib and glaucoma in both possibly POAG and normal-tension glaucoma.

Diabetes and type 2 diabetes mellitus have been previously reported to be associated with glaucoma development using the same Korean National Health Insurance Service data [20, 21]. Diabetes is affected by several factors, including oxidative stress [42], advanced glycation end products [43], and obstructed retrograde axonal flow of RGCs [44]. Of these, oxidative stress could be affected by systemic vascular disorders such as A-fib. In this study, comorbidity of diabetes was significantly associated with the development of glaucoma (HR: 1.30, $P < 0.001$). Diabetes mellitus can induce structural and functional injuries to small blood vessels, thus causing microvascular circulatory impairment of the optic nerve and retina [45]. Besides these vascular alterations, diabetes mellitus can damage retinal physiological functions of the glia and neurons. These mechanisms might have influenced results of higher incidence of glaucoma in those with comorbidity of diabetes in our study. In a recent population-based cohort study, superior and inferior peripapillary RNFL was significantly thinner among those with higher HbA1c levels and/or diabetes [46]. These findings also suggest possible clinical relationship between diabetes and glaucoma.

In a recent study using the same Korean National Health Insurance Service dataset, we have found a significant association between chronic renal disease and following development of glaucoma after adjusting for potential confounding factors [47]. Another study using the Korean National Health and Nutrition Examination Survey of 2010–2011, a cross-sectional population-

Table 2. Univariable Cox Hazard Proportion Analysis for the overall incidence of glaucoma.

	Glaucoma		Univariable Cox	
	No event (*N* = 50,524)	**Event (*N* = 1,593)**	**HR (95% CI)**	***P* value**
Group				
Control	42,069 (97.04)	1283 (2.96)	1.00	
A-fib	8455 (96.46)	310 (3.54)	1.362 (1.203,1.542)	<0.0001
Hypertension				
No	34,981 (97.4)	934 (2.6)	1.00	
Yes	15,543 (95.93)	659 (4.07)	1.83 (1.656, 2.023)	<0.0001
Diabetes mellitus				
No	41,167 (97.27)	1154 (2.73)	1.00	
Yes	9357 (95.52)	439 (4.48)	1.946 (1.742, 2.173)	<0.0001
Chronic renal failure				
No	50,131 (96.97)	1565 (3.03)	1.00	
Yes	393 (93.35)	28 (6.65)	3.071 (2.113, 4.463)	<0.0001
Hyperlipidaemia				
No	42,413 (97.18)	1230 (2.82)	1.00	
Yes	8111 (95.72)	363 (4.28)	1.712 (1.523, 1.926)	<0.0001
Age group (year)				
<50	14,086 (98.93)	153 (1.07)	1.00	
50–59	8963 (96.9)	287 (3.1)	2.996 (2.462, 3.645)	<0.0001
60–69	12,547 (95.54)	586 (4.46)	4.508 (3.773, 5.385)	<0.0001
70–79	10,040 (95.53)	470 (4.47)	5.251 (4.375, 6.303)	<0.0001
≥80	4888 (98.05)	97 (1.95)	3.144 (2.436, 4.057)	<0.0001
Sex				
Male	25,964 (97)	804 (3)	1.00	
Female	24,560 (96.89)	789 (3.11)	1.013 (0.919, 1.118)	0.7899
Residence				
Seoul (metropolitan)	9711 (96.31)	372 (3.69)	1.00	
2nd area	2757 (96.87)	89 (3.13)	0.881 (0.699, 1.111)	0.284
3rd area	3439 (97.01)	106 (2.99)	0.822 (0.663, 1.021)	0.0759
4th area	34,617 (97.12)	1026 (2.88)	0.782 (0.695, 0.88)	<0.0001
Household income				
0–30%	10,828 (97.06)	328 (2.94)	1.00	
30–70%	17,289 (97.23)	493 (2.77)	0.918 (0.798, 1.056)	0.2305
70–100%	22,407 (96.67)	772 (3.33)	1.125 (0.989, 1.28)	0.0735

A-fib atrial fibrillation.
Based on the results of all the univariable Cox Hazard Proportion Analysis model, we adjusted the confounding factors and performed a multivariable Cox proportional hazard regression analysis.
Percent proportion is indicated in () except for the 95% confidence interval.

based study including more than 4000, has shown that low renal function as a low estimated glomerular filtration rate is associated with POAG [48]. These results were concordant with the present study showing that comorbidity of chronic renal failure was significantly associated with subsequent development of glaucoma in our A-fib case-control study (HR: 1.97, $P < 0.001$).

The prevalence of glaucoma was significantly higher in older age groups compared to the group of those younger than 50 years old (all $P < 0.001$). Since glaucoma is an age-dependent disease and the prevalence of glaucoma increases with age as reported in many population-based studies worldwide [49], the results of our study seem reasonable.

Patients with A-fib already have systemic disorder and many A-fib patients have comorbidity of hypertension or diabetes. Thus, they already have a high risk of hypertensive or diabetic retinopathy, which could lead to visual loss. Additional vision-threatening diseases such as glaucoma could deteriorate patients' quality of life [17, 18]. Near and distant activities, peripheral vision, and driving are all influenced by glaucomatous visual defects, even with good visual acuity [17, 18]. Glaucoma also affects motor disturbances such as falling, which could lead to another medical treatment. Thus, medical burden might be aggravated during the lifetime [19]. Therefore, it may be important for physicians or cardiologists to consider referring these A-fib patients to ophthalmologists, especially to glaucoma specialists for proper evaluation and management to prevent further visual impairment and medical complications.

The strength of this study was that it included a large number of subjects with a long-term follow-up of 12 years. To the best of our knowledge, studies that investigate glaucoma development following A-fib using Korean National Health Insurance Service data have not been reported yet.

Table 3. Multivariable Cox Hazard Proportion Analysis for the overall incidence of glaucoma by modeling.

Variables	Model 1		Model 2		Model 3		Model 4	
	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Group								
Control	1.00		1.00		1.00		1.00	
Case	1.4 (1.24–1.59)	<0.001	1.3 (1.15–1.48)	<0.001	1.32 (1.16–1.5)	<0.001	1.31 (1.15–1.48)	<0.001
Hypertension								
No			1.00				1.00	
Yes			1.08 (0.97–1.22)	0.168			1.09 (0.97–1.22)	0.167
Diabetes mellitus								
No			1.00		1.00		1.00	
Yes			1.3 (1.15–1.48)	<0.001	1.33 (1.18–1.5)	<0.001	1.3 (1.15–1.47)	<0.001
Hyperlipidaemia								
No			1.00		1.00		1.00	
Yes			1.11 (0.97–1.26)	0.136	1.13 (1–1.29)	0.059	1.1 (0.97–1.26)	0.144
Chronic renal failure								
No			1.00		1.00		1.00	
Yes			1.99 (1.36–2.9)	<0.001	2.02 (1.38–2.95)	<0.001	1.97 (1.35–2.89)	<0.001
Age group (year)								
<50	1.00		1.00		1.00		1.00	
50–59	3 (2.47–3.65)	<0.001	2.78 (2.28–3.39)	<0.001	2.81 (2.3–3.42)	<0.001	2.78 (2.28–3.39)	<0.001
60–69	4.54 (3.8–5.42)	<0.001	4.05 (3.37–4.86)	<0.001	4.13 (3.45–4.95)	<0.001	4.05 (3.37–4.86)	<0.001
70–79	5.33 (4.44–6.4)	<0.001	4.66 (3.85–5.63)	<0.001	4.79 (3.97–5.77)	<0.001	4.63 (3.83–5.61)	<0.001
≥80	3.22 (2.5–4.16)	<0.001	2.91 (2.25–3.77)	<0.001	3 (2.32–3.87)	<0.001	2.91 (2.25–3.78)	<0.001
Sex								
Male	1.00						1.00	
Female	0.96 (0.87–1.05)	0.364					0.96 (0.87–1.06)	0.405
Residence								
Seoul (metropolitan)			1.00		1.00		1.00	
2nd area			0.84 (0.66–1.05)	0.13	0.84 (0.66–1.05)	0.13	0.84 (0.67–1.06)	0.145
3rd area			0.84 (0.68–1.05)	0.126	0.84 (0.68–1.05)	0.121	0.85 (0.68–1.05)	0.136
4th area			0.81 (0.72–0.92)	<0.001	0.81 (0.72–0.91)	<0.001	0.82 (0.73–0.92)	<0.001
Household income								
0–30%							1.00	
30–70%							0.96 (0.83–1.1)	0.569
70–100%							1.05 (0.92–1.2)	0.445
Model criterion value	AUC: 0.649; AIC: 33288.08		AUC: 0.664; AIC: 33236.13		AUC: 0.663; AIC: 33236.03		AUC: 0.665; AIC: 33238.82	

AUC Area Under the Curve, *AIC* Akaike's Information Criterion, the model with the largest AUC or lowest AIC value being considered the best.

This study has several limitations. The most important one was the potential incorrectness of the diagnosis of A-fib and glaucoma based on KCD codes. However, several published papers have used Korean National Health Insurance claims data for glaucoma [20–22, 50–53]. Furthermore, the cumulative incidence of glaucoma in the control group consistently increased for 11 years as shown in Fig. 1c. This might partly indicate the validity of the glaucoma diagnosis in this study. Second, glaucoma might have been underdiagnosed and underreported because it might be asymptomatic until a relatively late stage. Hence, diagnosis of glaucoma is often delayed or missed at an early stage because of delayed visits to ophthalmologists. These cases might have belonged to the non-glaucoma event group. Thus, the real HR might be greater than the HR presented in this study. Third, glaucoma diagnoses were not subclassified according to its subtypes. The KCD code-based diagnosis does not always reflect the correct cause of glaucoma because gonioscopy or anterior segment optical coherence tomography is not consistently used to distinguish angle status. Since IOP is also not always measured with Goldmann applanation tonometry, it is difficult to discriminate normal tension glaucoma with only the KCD code. In this regard, we included overall glaucoma with KCD code-based diagnosis. However, mechanisms of the included glaucoma may be different according to subtypes of glaucoma. Regarding other limitations of our study, the following should be mentioned. First, other data of health examinations, such as body mass index, smoking, and alcohol status, were only partially included. In this aspect, these potential confounding factors could not be adjusted. Second, there was a higher probability of bias for control group patients from the health insurance data than for healthy control

Table 4. Cumulative incidence rate (%) of glaucoma during the follow-up period of 11 years.

	N	Event	Cumulative incidence rate (%) at 1 year	Cumulative incidence rate (%) at 2 years	Cumulative incidence rate (%) at 3 years	Cumulative incidence rate (%) at 4 years	Cumulative incidence rate (%) at 5 years	Cumulative incidence rate (%) at 6 years	Cumulative incidence rate (%) at 7 years	Cumulative incidence rate (%) at 8 years	Cumulative incidence rate (%) at 9 years	Cumulative incidence rate (%) at 10 years	Cumulative incidence rate (%) at 11 years
Total	52,117	1593	0.42 (0.36, 0.47)	0.80 (0.73, 0.88)	1.19 (1.09, 1.28)	1.61 (1.50, 1.72)	1.98 (1.85, 2.10)	2.36 (2.22, 2.49)	2.79 (2.64, 2.93)	3.16 (2.99, 3.32)	3.51 (3.33, 3.70)	4.01 (3.79, 4.23)	4.37 (4.07, 4.67)
Group													
Control	43,352	1283	0.39 (0.33, 0.45)	0.76 (0.68, 0.84)	1.12 (1.02, 1.22)	1.53 (1.41, 1.65)	1.88 (1.75, 2.01)	2.28 (2.14, 2.43)	2.68 (2.52, 2.84)	3.02 (2.84, 3.19)	3.33 (3.14, 3.52)	3.76 (3.53, 3.98)	4.02 (3.75, 4.30)
A-fib	8765	310	0.53 (0.38, 0.69)	1.02 (0.80, 1.24)	1.55 (1.27, 1.82)	2.06 (1.74, 2.38)	2.49 (2.13, 2.84)	2.75 (2.38, 3.12)	3.36 (2.94, 3.78)	3.92 (3.45, 4.39)	4.53 (3.99, 5.07)	5.47 (4.77, 6.17)	6.42 (5.09, 7.74)

A-fib atrial fibrillation.
Kaplan–Meier analysis.
95% confidence interval is indicated in ().

patients from the general population who are not registered in health insurance data without having received any medical care. Third, potential ethnic discrepancies might exist in other ethnic groups than in this Korean population, which was not regarded in the present study.

In conclusion, A-fib was significantly associated with glaucoma development after adjusting for potential confounding factors. Thus, physicians may need to pay careful attention to patients with A-fib, especially those with comorbidities of diabetes and chronic renal failure. These patients should be referred to ophthalmologists for glaucoma screening to avoid potential impairment of vision. Population-based multicentre studies are needed for a definitive judgment.

SUMMARY

What was known before

- The association of higher risk of glaucoma in those with diabetes and hypertension (well-known cardiovascular risk factors) than those without were reported using Korean National Health Insurance Service data.

What this study adds

- The association between cardiovascular disease, especially atrial fibrillation, and the risk of glaucoma development using Korean National Health Insurance Service data has not been reported yet. The present study reveals that atrial fibrillation was significantly associated with the development of glaucoma after adjusting for potential confounding factors in 12 year longitudinal national cohort.

DATA AVAILABILITY

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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AUTHOR CONTRIBUTIONS

HC, JH, and JAC contributed to the design of this study; HC, JH, JAC, JC, and RK conducted this study; HC, JH, JAC, JC, and RK contributed to data collection, analysis, management, and interpretation; HC, JH, and JC, and JC prepared the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

This study adhered to the tenets of the Declaration of Helsinki. NHIS-NCS 2002–2013 project was approved by the Institutional Review Board (IRB) of the Korean National Health Insurance Service. This study was approved by the Institutional Review Board of Gyeongsang National University Changwon Hospital and School of Medicine. The requirement for informed consent was exempted by the IRB because this study was retrospective in nature.

ADDITIONAL INFORMATION

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