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Atrial Fibrillation Increases the Risk of Peripheral Arterial Disease With Relative Complications and Mortality

A Population-Based Cohort Study

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Abstract: Atrial fibrillation (AF), an increasing prevalent cardiac arrhythmia due to aging general population, has many common risk factors with peripheral arterial disease (PAD). However, it is unclear whether AF is associated with a risk of PAD. We investigated the prevalence of AF and PAD in the general population and the risk of PAD among the AF population.

This longitudinal, nationwide, population-based cohort study was conducted using data from the Taiwan National Health Insurance Research Database recorded during 2000 to 2011. In total, 3814 and 15,364 patients were included in the AF and non-AF cohorts, respectively. Univariate and multivariate Cox proportional hazard regression models were used for examining the effects of AF on the risk of outcomes.

The average follow-up periods of PAD were 4.96 ± 3.28 and 5.29 ± 3.35 years for the AF and non-AF cohorts, respectively. Overall, the risk of PAD showed a significantly higher risk in the AF cohort (adjusted HR=1.31, 95% CI=1.19–1.45) compared with the non-AF cohort. Similar results were observed for heart failure and stroke, where the AF cohort had a 1.83-fold and 2.53-fold higher risk of developing heart failure and stroke. The AF cohort also had a significant increased risk for mortality (adjusted HR=1.66, 95% CI=1.49–1.84).

The present study indicated that the incidence of PAD, heart failure, stroke, and overall mortality is higher in patients with AF than in those without it.

(*Medicine* 95(9):e3002)

Abbreviations: AF = atrial fibrillation, aHR = adjusted hazard ratio, BNHI = Bureau of National Health Insurance, CI = confidence interval, LHID 2000 = Longitudinal Health Insurance Database 2000, NHI = National Health Insurance, NHIA = National Health Insurance Administration, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes, PAD = peripheral arterial disease.

Editor: Jimmy Efird.
Received: November 3, 2015; revised: February 8, 2016; accepted: February 11, 2016.
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Funding: this study is supported in part by Taiwan Ministry of Health and Welfare Clinical Trial and Research Center of Excellence (MOHW105-TDU-B-212-133019), China Medical University Hospital, Academia Sinica Taiwan Biobank Stroke Biosignature Project (BM10501010037), NRPB Stroke Clinical Trial Consortium (MOST 104-2325-B-039 -005), Tseng-Lien Lin Foundation, Taichung, Taiwan, Taiwan Brain Disease Foundation, Taipei, Taiwan, and Katsuzo and Kiyo Aoshima Memorial Funds, Japan;and CMU under the Aim for Top University Plan of the Ministry of Education, Taiwan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. No additional external funding received for this study.
The authors have no conflicts of interest to disclose.
M-CL and C-HK equally contributory to this study.

ISSN: 0025-7974
DOI: 10.1097/MD.0000000000003002

INTRODUCTION

Atrial fibrillation (AF) is a common cardiac arrhythmia inclinical practice, and its prevalence rate significantly increases with age.[1] AF leads to a higher rate of ischemic stroke, heart failure, and vascular death, increasing the morbidity and mortality rates.[2–5] Vascular complications and AF share many common risk factors, including age, smoking status, obesity, diabetes, and hypertension.[4,6] Recent evidence has revealed similarities, such as inflammation, endothelial injury, and fulfillment of Virchow's triad, between the pathogenesis of thrombogenesis among patients with AF and atherothrombosis.[7,8]

Peripheral arterial disease (PAD), the third leading cause of atherosclerotic vascular morbidity, has many risk factors common with AF. Both PAD and AF are increasingly prevalent in elderly patients and have a higher rate of vascular events, including stroke and myocardial infarction (MI), compared with the general population.[9,10] PAD is often asymptomatic; however, asymptomatic PAD confers a high risk of vascular events or mortality.[11] Based on different populations and comorbidities, some observational studies have revealed a high prevalence of PAD (12.2% to 16.8%) in the AF population.[12–14] Therefore, more information is required on the prevalence of PAD among patients with AF in the general population and its association with and differences from other major comorbidities.

The aim of this nationwide population-based study was to analyze the prevalence of PAD among patients with AF in the general population and determine whether these patients are at a higher risk of PAD and other comorbidities.

METHODS

Data Source

In this retrospective cohort study, medical records were retrieved from the Longitudinal Health Insurance Database 2000 (LHID2000) (http://nhird.nhri.org.tw/en/Data_Subsets.html#S3). In 1995, the National Health Insurance (NHI) program, a government-run, single-payer insurance system, was established in Taiwan. All Taiwanese residents are obligated to enroll in the NHI program, which covers >99% of the Taiwanese population (http://www.nhi.gov.tw/). The LHID2000 comprises the claims data and registration files of 1,000,000 patients randomly sampled from the 2000 Registry for Beneficiaries of the Taiwan NHI program. The National Health Research Institute reportedno significant differences in sex, age, and health care cost distributions between patients in the LHID2000 and all enrollees and beneficiaries. The diagnostic codes used were based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH-104-REC2-115). The IRB also specifically waived the consent requirement.

Patients

We selected 6764 patients with newly diagnosed AF (ICD-9-CM code 427.3) during 2000 to 2011. These patients had complete age or sex information, but were not previously diagnosed with PAD (ICD-9-CM codes 440.2, 440.3, 440.8, 440.9, and 443), heart failure (ICD-9-CM code 428), and stroke (ICD-9-CM codes 430–438). The date of AF diagnosis was defined as the index date. Four patients without AF were frequency-matched with each patient in the AF cohort with respect to age (in 5-year intervals), sex, and the year of the index date. In the non-AF cohort, patients with a history of AF, PAD, heart failure, and stroke before the index date or incomplete data on age or sex were excluded and replaced with qualifying patients. Finally, 3841 and 15,364 patients were included in the AF and non-AF cohorts, respectively.

Outcome and Comorbidity

Patients in both cohorts were monitored from the index date until a new diagnosis of PAD, heart failure, stroke, or death or until they were censored because of loss to follow-up, withdrawal from the insurance system, or the end of follow-up on December 31, 2011.

We considered diabetes (ICD-9-CM code 250), hypertension (ICD-9-CM codes 401–405), hyperlipidemia (ICD-9-CM code 272), chronic obstructive pulmonary disease (COPD; ICD-9-CM codes 491, 492, and 496) and coronary artery disease (CAD; ICD-9-CM codes 410–414) as pre-existing comorbidities that were potential confounders in the association between AF and outcomes.

Statistical Analysis

The distributions of categorical demographic factors and comorbidities, namely sex, age (≤64 years, 65–74 years, and 75 years), diabetes, hypertension, hyperlipidemia, COPD, CAD, and asthma, were compared between the AF and non-AF cohorts. Differences were examined using the chi-squared and t tests for categorical and continuous variables, respectively.

Furthermore, the cumulative incidence Kaplan–Meier curves of the 2 cohorts were compared using the log rank test. The incidence of outcomes (per 1000 person-years) was estimated for each cohort by using the associated demographic variables and comorbidities. Univariate and multivariate Cox proportional hazard regression models were used for examining the effects of AF on the risk of outcomes; results are shown as hazard ratios (HRs) with 95% confidence intervals (CIs). The multivariate model was used for adjusting several variables such as sex; age; and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, CAD, and asthma. Data processing and statistical analyses were performed using the SAS statistical software (Version 9.3 for Windows; SAS Institute, Inc, Cary, NC). A 2-tailed P value of 0.05 was considered significant.

RESULTS

The distributions of the demographic variables and comorbidities of the AF and non-AF cohorts are shown in Table 1. The proportion of men was higher than that of women (58.0% vs 42.1%). The mean (± standard deviation) age of the AF cohort was 66.8 (±13.4) years, and that of the non-AF cohort was 65.9 (±13.5) years, with 39.8% of all patients aged ≤ 64 years. Comorbidities were more likely to occur in the AF cohort than in the non-AF cohort ($P < 0.001$).

The average follow-up periods of PAD were 4.96 ± 3.28 and 5.29 ± 3.35 years for the AF and non-AF cohorts, respectively. Overall, the patients with AF had higher incidence density rates of PAD (6.87 vs 4.06 per 1000 person-years), heart failure (50.7 vs 6.91 per 1000 person-years), stroke (40.0 vs 13.9 per 1000 person-years), and overall mortality (26.5 vs 15.8 per 1000 person-years) than the non-AF cohort, with an crude hazard ratio (cHR) of 1.69 (95% CI=1.54–1.86), 7.06 (95% CI=6.34–7.86), 2.86 (95% CI=2.61–3.15), and 1.69 (95% CI = 1.53–1.87) (Table 2). Multivariable Cox proportional hazard regression analysis for the risk of PAD showed a significantly higher risk in the AF cohort (adjusted HR = 1.31, 95% CI = 1.19–1.45) compared with the non-AF cohort. Similar results were observed for heart failure and stroke, where the AF cohort had a 1.83-fold and 2.53-fold higher risk of developing heart failure and stroke. Compared with the non-AF cohort, the AF cohort had a significant increased risk for mortality (adjusted HR = 1.66, 95% CI = 1.49–1.84).

The overall incidence and risk of PAD, heart failure, stroke and mortality in the 2 cohorts were compared with respect to several variables, namely sex, and age (Table 3). The sex-specific AF cohort to non-AF cohort relative risk of PAD were significantly higher for both women (adjusted HR = 1.21, 95% CI = 1.04–1.40) and men (adjusted HR = 1.39, 95% CI = 1.22–1.58). The incidence was increased with age in both cohorts. The relative risk of PAD on the age-specific AF cohort to non-AF cohort was higher in the group of aged ≤ 64 and in aged ≥ 75. The risks of heart failure, stroke, and mortality, in all stratifications, remained higher in the AF cohort than in the non-AF cohort.

Relative to patients in the non-AF cohort without comorbidity, patients in the AF cohort with comorbidity had a higher risk of heart failure (adjusted HR = 16.1, 95% CI = 12.8–20.2) than that of patients with only comorbidity (adjusted HR = 2.88, 95% CI = 2.27–3.65) (Table 4, P value of interaction < 0.001) (Table 4). Furthermore, patients with both AF and comorbidity exhibited a significantly higher risk of stroke than that of

TABLE 1. Comparison of Demographic Characteristics and Comorbidities in Patients With and Without Atrial Fibrillation

	Atrial Fibrillation		
	No (N = 15364)	Yes (N = 3841)	*P* Value
Sex			0.99
Women	6460 (42.1)	1615 (42.1)	
Men	8904 (58.0)	2226 (58.0)	
Age stratified			0.99
≤ 64	6116 (39.8)	1529 (39.8)	
65–74	4516 (29.4)	1129 (29.4)	
75+	4732 (30.8)	1183 (30.8)	
Age, mean ± SD*	65.9 (13.5)	66.8 (13.4)	<0.001
Comorbidity			
Diabetes	1951 (12.7)	580 (15.1)	<0.001
Hypertension	7220 (47.0)	2690 (70.0)	<0.001
Hyperlipidemia	4073 (26.5)	1233 (32.1)	<0.001
COPD	2612 (17.0)	983 (25.6)	<0.001
CAD	3489 (22.7)	2021 (52.6)	<0.001

Chi-square test
CAD = coronary artery disease, COPD = chronic obstructive pulmonary disease, SD = standard deviation.
* *t* test.

patients without both conditions (adjusted HR = 4.63, 95% CI = 3.98–5.39). We observed a significantly higher risk of PAD for patients with AF and comorbidity (adjusted HR = 3.89, 95% CI = 2.82–5.36) than for those without AF and comorbidity. Table 4 also shows that the AF patients with comorbidity had the significantly higher risk of mortality (adjusted HR = 1.82, 95% CI = 1.58–2.09), compared with that of the patients without AF and without comorbidity.

Figure 1A toD shows that the AF cohort had a significantly higher cumulative proportion of PAD ($P < 0.001$) (Figure 1A), heart failure ($P < 0.001$) (Figure 1B), stroke ($P < 0.001$) (Figure 1C), and mortality ($P < 0.001$) (Figure 1D) compared with the non-AF cohort.

DISCUSSION

In this nationwide population-based study, we observed that the risk of PAD was significantly higher in the AF cohort (adjusted HR = 1.58, 95% CI = 1.32–1.88) compared with the non-AF cohort. The risk of PAD increased with age and comorbidity in both cohorts. Patients with both AF and comorbidities exhibited a higher prevalence of developing PAD; however, AF remained an independent risk factor for PAD after adjustment for covariates.

Previous studies have shown conflicting results regarding the association between AF and PAD.[15]In the Women's Health Initiative study, PAD was independently associated with the development of AF in postmenopausal women.[16] A retrospective study by Naccarelli et al revealed that the prevalence of PAD was >2-fold higher in patients with AF than in those without AF.[17]This result is in accordance with the results of our study.

Patients with AF often have coexisting vascular diseases, and the combination of the 2 diseases substantially increases the risk of future cardiovascular events. Therefore, we suggest that

TABLE 2. Comparison of Incidence Densities of Outcome (Hazard Ratio) Between Patients With and Without Atrial Fibrillation

	Atrial Fibrillation							
	No			Yes				
	Event	PY	Rate†	Event	PY	Rate†	Crude HR‡ (95% CI)	Adjusted HR§ (95% CI)
Peripheral arterial disease	330	81,349	4.06	131	19,058	6.87	1.69 (1.54, 1.86)*	1.31 (1.19, 1.45)*
Heart failure	559	80,900	6.91	831	16,387	50.7	7.06 (6.34, 7.86)*	1.83 (1.63, 2.05)*
Stroke	1115	79,982	13.9	709	17,706	40.0	2.86 (2.61, 3.15)*	2.53 (2.29, 2.80)*
Mortality	1313	82,990	15.8	524	19,777	26.5	1.69 (1.53, 1.87)*	1.66 (1.49, 1.84)*

CI = confidence interval, HR = hazard ratio, PY = person-years.
† Rate, incidence rate, per 1000 person-years
‡ Crude HR, relative hazard ratio;
§ Adjusted HR: multiple analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, and CAD;|| Comorbidity: patients with any one of the comorbidities diabetes, hypertension, hyperlipidemia, COPD, CAD, and asthma were classified as the comorbidity group.
* $P < 0.001$

TABLE 3. Comparison of Incidence Densities of Outcome (Hazard Ratio) Between Patients With and Without Atrial Fibrillation by Demographic Characteristics and Comorbidities

	Atrial Fibrillation							
	No			Yes				
	Event	PY	Rate†	Event	PY	Rate†	Crude HR‡ (95% CI)	Adjusted HR§ (95% CI)
Peripheral arterial disease								
Sex								
Women	136	34218	3.97	53	7943	6.67	1.68 (1.45, 1.94)**	1.21 (1.04, 1.40)*
Men	194	47131	4.12	78	11115	7.02	1.70 (1.51, 1.93)**	1.39 (1.22, 1.58)*
Stratify age								
≤ 64	85	35217	2.41	44	8496	5.18	2.15 (1.85, 2.48)**	1.37 (1.17, 1.60)**
65–74	141	25105	5.62	47	5890	7.98	1.42 (1.19, 1.69)**	1.15 (0.96, 1.37)
75+	104	21027	4.95	40	4672	8.56	1.73 (1.46, 2.06)**	1.41 (1.18, 1.68)**
Heart failure								
Sex								
Women	269	33846	7.95	386	6710	57.5	6.91 (5.91, 8.08)**	5.85 (4.96, 6.91)**
Men	290	47055	6.16	445	9678	46.0	7.22 (6.23, 8.37)**	5.96 (5.09, 6.99)**
Stratify age								
≤ 64	87	35252	2.47	257	7571	34.0	13.4 (10.5, 17.0)**	10.5 (8.05, 13.6)**
65–74	199	25033	7.95	259	5049	51.3	6.27 (5.21, 7.54)**	4.95 (4.06, 6.05)**
75+	273	20616	13.2	315	3768	83.6	5.97 (5.07, 7.03)**	5.16 (4.35, 6.11)**
Stroke								
Sex								
Women	434	33815	12.8	327	7308	44.8	3.47 (3.00, 4.00)**	3.03 (2.61, 3.53)**
Men	681	46168	14.8	382	10398	36.7	2.49 (2.19, 2.82)**	2.21 (1.94, 2.53)**
Stratify age								
≤ 64	183	35041	5.22	163	8128	20.1	3.86 (3.12, 4.77)**	2.85 (2.25, 3.60)**
65–74	381	24682	15.4	246	5405	45.5	2.94 (2.51, 3.45)**	2.59 (2.18, 3.07)**
75+	551	20260	27.2	300	4172	71.9	2.66 (2.31, 3.06)**	2.37 (2.05, 2.74)**
Mortality								
Sex								
Women	456	34928	13.1	198	8217	24.1	1.87 (1.58, 2.20)**	1.76 (1.47, 2.09)**
Men	857	48061	17.8	326	11560	28.2	1.59 (1.40, 1.81)**	1.60 (1.40, 1.83)**
Stratify age								
≤ 64	160	35637	4.49	94	8739	10.8	2.41 (1.87, 3.11)**	1.99 (1.49, 2.64)**
65–74	396	25811	15.3	148	6181	23.9	1.58 (1.31, 1.91)**	1.45 (1.19, 1.78)**
75+	757	21543	35.1	282	4857	58.1	1.70 (1.48, 1.95)**	1.70 (1.47, 1.96)**

CI = confidence interval, HR = hazard ratio, PY = person-years.
† Rate, incidence rate, per 1000 person-years
‡ Crude HR, relative hazard ratio
§ Adjusted HR: multiple analysis including age, sex, and comorbidities of diabetes, hypertension, hyperlipidemia, COPD, and CAD
* $P < 0.05$,
** $P < 0.001$.

atherothrombosis is the mechanism underlying the significant association between AF and PAD. In addition, the results of the present study imply that overlapping of the thrombogenesis pathway involving endothelial damage, inflammation activation, and hypercoagulability connects AF and PAD. Furthermore, the fulfillment of Virchow's triad possibly explains the increasing risk of stroke and cardiovascular disease development in patients with AF and might also contribute to the pathophysiology of PAD.[6,8] The ACC/AHA/ESC 2006 guidelines emphasized the endothelial dysfunction, stasis, and elevated levels of P-selectin and von Willebrand factor in patients with AF. Levels of fibrin, D-dimer, and C-reactive protein, which may lead to a hypercoagulable state and the aforementioned multiple comorbidities, are also higher in patients with AF.[18,19]

The association of AF with PAD has gained attention. It is well established that PAD independently predicts stroke in patients with AF and consequently is included as a component of the CHA2DS2-VASc score.[20] In a review article, the previous studies emphasized the mechanism and summarized that AF coexisting with PAD leads to frequent CV outcomes and that patients with AF should be routinely screened for the presence of PAD.[21,22] In accordance with previous evidence, our results revealed that PAD often coexisted with AF. Therefore, screening for asymptomatic PAD and decision-making for thromboprophylaxis is crucial.[23]

TABLE 4. Cox Proportional Hazard Regression Model for Analyzing the Risk of Atrial-Fibrillation-Associated Outcome With the Interaction Effects of Comorbidity

	Variables	Event	PY	Rate†	Adjusted HR‡ (95% CI)	*P* Value§
Peripheral arterial disease						
Atrial fibrillation	Comorbidity‖					0.43
−	−	56	33,730	1.66	1 (Reference)	
−	+	274	47,619	5.75	2.88 (2.14, 3.87)**	
+	−	10	2861	3.50	2.29 (1.17, 4.49)*	
+	+	121	16,198	7.47	3.89 (2.82, 5.36)**	
Heart failure						
Atrial fibrillation	Comorbidity‖					<0.001
−	−	82	33,674	2.44	1 (Reference)	
−	+	477	47,226	10.1	2.88 (2.27, 3.65)**	
+	−	86	2505	34.3	16.1 (11.9, 21.7)**	
+	+	745	13,882	53.7	16.1 (12.8, 20.2)**	
Stroke						
Atrial fibrillation	Comorbidity‖					0.24
−	−	226	33,365	6.77	1 (Reference)	
−	+	889	46,618	19.1	1.83 (1.57, 2.12)**	
+	−	49	2712	18.1	3.27 (2.40, 4.46)**	
+	+	660	14,994	44.0	4.63 (3.98, 5.39)**	
Mortality						
Atrial fibrillation	Comorbidity‖					0.31
−	−	352	33,976	10.4	1 (Reference)	
−	+	961	49,015	19.6	1.14 (1.00, 1.29)*	
+	−	51	2900	17.6	2.19 (1.63, 2.93)**	
+	+	473	16,877	28.0	1.82 (1.58, 2.09)**	

CI = confidence interval, HR = hazard ratio, PY = person-years.
† Rate, incidence rate, per 1000 person-years.
‡ Adjusted HR: multiple analysis including age and sex.
§ *P* value for interaction.
‖ Comorbidity: patients with any one of the comorbidities diabetes, hypertension, hyperlipidemia, COPD, CAD, and asthma were classified as the comorbidity group.
* $P < 0.05$
** $P < 0.001$.

Antiplatelet therapy is effective for reducing the mortality and morbidity of PAD, whereas oral anticoagulation therapy with warfarin is not beneficial and is potentially harmful because of an increased risk of major bleeding. To our knowledge, no robust clinical trials have examined the benefits and risks of new antithrombotic medications in patients with PAD. By contrast, the use of anticoagulant drugs or vitamin K antagonist therapy is recommended in patients with a high risk of AF, and novel oral anticoagulant drugs provide a new option.[24] Patients with AF having a high risk of PAD or those with PAD seem to be a fragile subgroup and have a substantial risk of atherothrombotic events; therefore, these patients must be carefully administered thromboprophylactic drugs or a combined antithrombotic therapy.

Many patients with AF commonly have associated atherosclerotic risk factors that may lead to ischemic stroke, myocardial infarction, increased risk of cardiovascular (CV) events, and mortality.[6,25,26] The result of a study by Li et al in 2015, which included 3737 patients with newly diagnosed AF and 704,225 patients without, showed that a significantly higher incidence of future major adverse cardiac events and mortality in the AF group. This study also evaluated the National Health Insurance Research Database for the relationship of AF and major cardiovascular events, and newly diagnosed AF patients were associated with 8.45 times the risk of developing future major adverse cardiac events than healthy participants.[27] Similar results were observed in our study, where the AF cohort had a 1.84-fold higher risk of developing heart failure.

The strength in our study is this study was the longitudinal cohort study from the population-based and nationwide database. The longitudinal designed study includes a very big case numbers of study and control cohorts to have a very low loss of follow-up. Besides, under the reimbursement law, the insurance system is only 1 buyer and operated by the Taiwan government. Therefore, the database can accurately represent the general Taiwan's population. Because the insurance claims in the database should be routinely surveyed by the medical specialists under anonymous peer review based on the standard diagnosed criteria. So, in this study, the diagnoses of PAD and AF by the ICD-9 codes should be highly reliable.

However, several limitations should be acknowledged. First, because each disease was defined on the basis of ICD-9-CM codes, we could not distinguish whether patients had chronic or paroxysmal AF; therefore, the prognosis of these conditions may differ. Furthermore, no laboratory markers were tested at the baseline; such tests could have facilitated accurate prediction of the severity of PAD. In the other hand, PAD may be often asymptomatic, and physicians may ignore it unless routine detection of PAD in AF patients was established.[28] Second, thromboprophylaxis, which is a potential confounding factor, was not

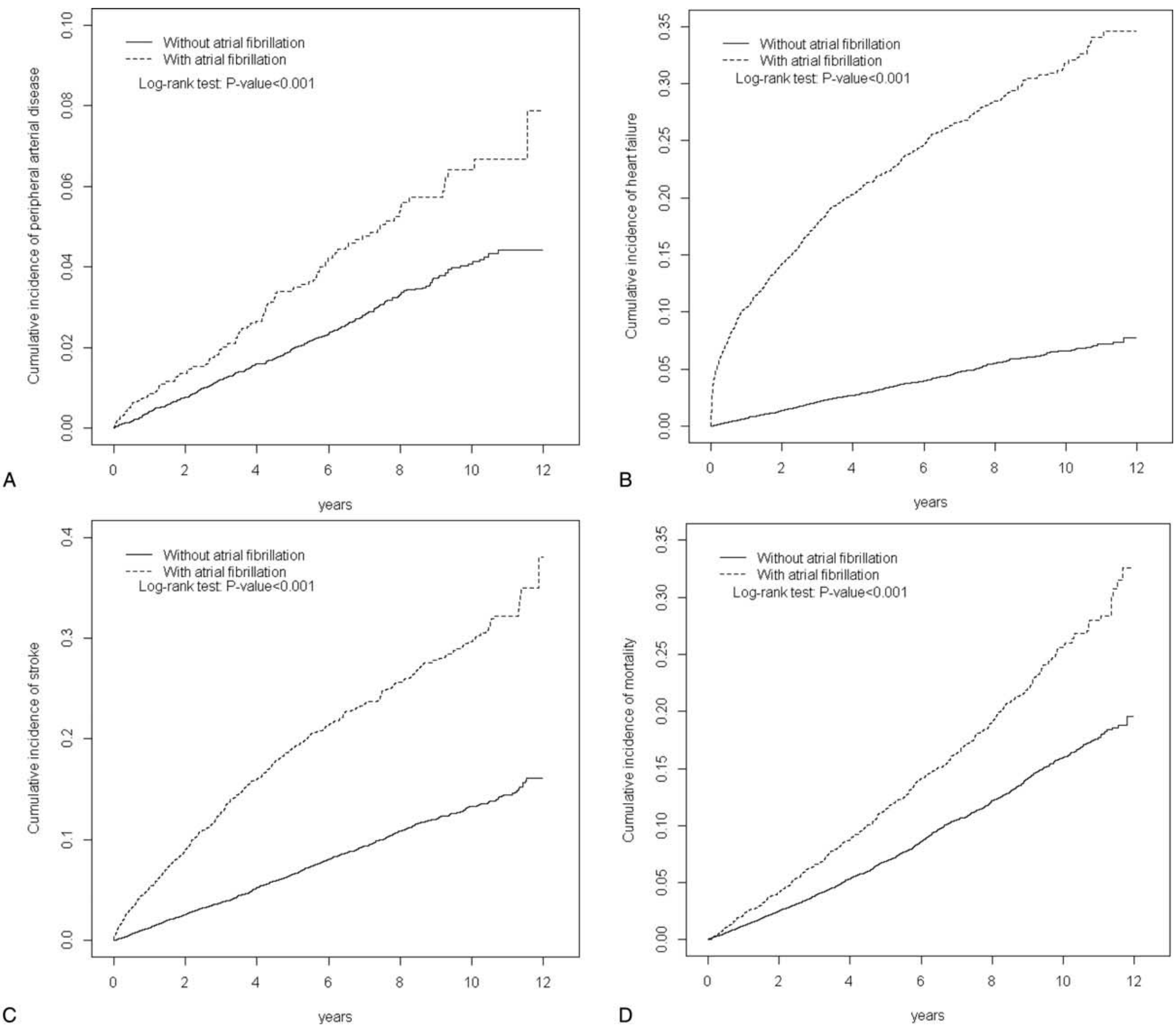

FIGURE 1. A–D show that the AF cohort had a significantly higher cumulative proportion of PAD ($P < 0.001$) (A), heart failure ($P < 0.001$) (B), stroke ($P < 0.001$) (C), and mortality ($P < 0.001$) (D) compared with the non-AF cohort. AF = atrial fibrillation; PAD = peripheral arterial disease.

considered. Differences in medication use affect the development of PAD. Finally, the NHI Research Database does not provide detailed information on patient characteristics, such as the blood pressure, fasting glucose or hemoglobin A1c, LDL cholesterol or total cholesterol, HDL cholesterol, BMI, smoking habit, medications, family history, alcohol consumption, lifestyle, laboratory data, and body mass index. However, we already used the related disease such as smoking-related diseases and diabetes, hypertension, and hyperlipidemia to do the possible adjustment. Despite these limitations, the data regarding the relationship between AF and PAD are highly reliable because of the validity of the database, large sample size, and long follow-up period.

In conclusion, we showed that the incidence of PAD is higher in patients with AF than in those without AF. Moreover, our results suggest that AF with comorbidities predisposed patients to a much higher risk of PAD. Future studies must focus on identifying high-risk subgroups according to the ABI index or imaging or laboratory studies. A large-scale clinical trial determining secondary prevention therapies in high-risk individuals is crucial for reducing mortality and cardiovascular events would be worthwhile.

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