The association between influenza infection, vaccination, and atrial fibrillation: A nationwide case-control study

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BACKGROUND Influenza infection could activate systemic inflammatory responses and increase the sympathetic tone that plays an important role in the pathogenesis of atrial fibrillation (AF).

OBJECTIVES The goal of the present study was to investigate whether influenza infection was a risk factor for AF. We also aimed to study whether influenza vaccination could decrease the risk of AF.

METHODS From 2000 to 2010, a total of 11,374 patients with newly diagnosed AF were identified from the Taiwan National Health Insurance Research Database. On the same date of enrollment, 4 control patients (without AF) with matched age and sex were selected to be the control group for each study patient. The relationship between AF and influenza infection or vaccination 1 year before the enrollment was analyzed.

RESULTS Compared with patients without influenza infection or vaccination (reference group; n = 38,353), patients with influenza infection without vaccination (n = 1369) were associated with a significantly higher risk of AF with an odds ratio of 1.182 ($P = .032$) after adjustment for baseline differences. The risk of AF was lower in patients receiving influenza vaccination without influenza infection (n = 16,452) with an odds ratio of 0.881 ($P < .001$). In patients who have received influenza vaccination and experienced influenza infection (n = 696), the risk of AF was similar to that in the reference group (odds ratio 1.136; $P = .214$). The lower risk of AF with vaccination was consistently observed in subgroup analyses.

CONCLUSION Influenza infection was significantly associated with the development of AF, with an 18% increase in the risk, which could be reduced through influenza vaccination.

KEYWORDS Atrial fibrillation; Influenza infection; Vaccination

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Background

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, accounting for frequent hospitalizations, hemodynamic abnormalities, and thromboembolic events.[1] The prevalence of AF is about 0.4%–1% in the general population, increasing with age.[2,3] It is associated with a 5-fold increased risk of ischemic stroke, 3-fold increased risk of heart failure, and 2-fold increased risk of both dementia and mortality.[1] Although the precise mechanisms of AF are not well understood, accumulating evidence indicated that inflammation and autonomic nervous system were involved in the pathogenesis of AF.[4–6] Many inflammatory biomarkers and mediators, such as C-reactive protein (CRP), tumor necrosis factor α (TNF-α), interleukin 2 (IL-2), IL-6, and IL-8, were reported to be higher in patients with AF.[5,6] In addition, sympathetic and parasympathetic nervous systems also play an important role in the initiation and perpetuation of AF.[7–9]

Influenza infection could cause significant morbidity and mortality, and it is a serious human health concern worldwide. Influenza infection not only results in the production of proinflammatory cytokines, such as IL-1β, IL-6, IL-18, and TNF-α,[10] but also activates the sympathetic nervous system,[11,12] which are all related to the occurrence of AF. Although influenza infection has been reported to be associated with an increased risk of myocardial infarction

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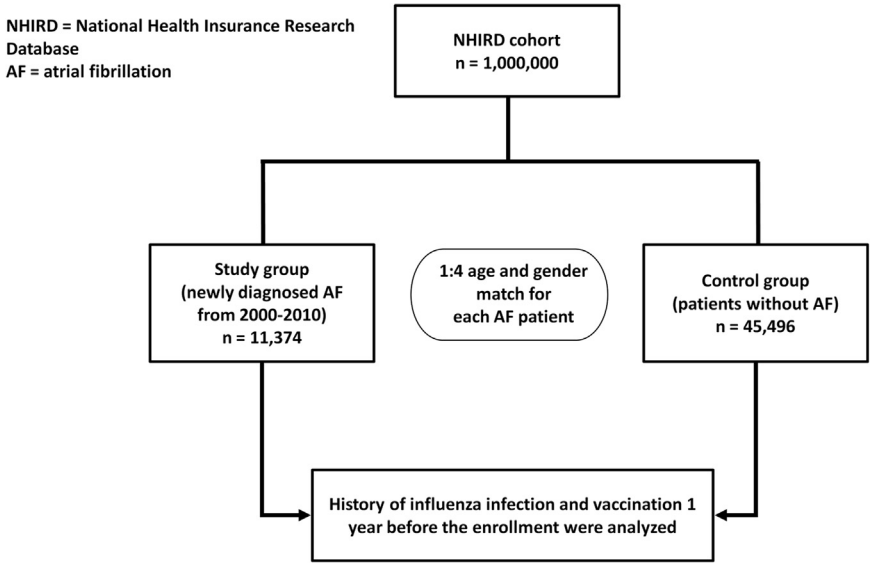

Figure 1 Flowchart of the enrollment of study patients. A total of 11,374 patients with AF were enrolled as the study group. The exposure to influenza infection and vaccination 1 year before the enrollment was analyzed and compared with that of patients without AF (control group; n = 45,496).

and stroke,[13,14] the relationship between influenza infection and AF has not been well studied previously. The goal of the present study was to investigate whether influenza infection was a risk factor for AF. We also aimed to study whether influenza vaccination, a useful way to reduce the risk of influenza infection, could decrease the risk of AF.

Methods

Database

This study used the National Health Insurance Research Database (NHIRD) released by the Taiwan National Health Research Institutes. The National Health Insurance (NHI) system is a mandatory universal health insurance program that offers comprehensive medical care coverage to all Taiwanese residents. The NHIRD was a cohort data set that contained all the medical claims data for 1,000,000 beneficiaries (mean age 34.8 ± 20.9 years; n = 513,876, 51.4% men), who were randomly sampled from the 25.68 million enrollees under the NHI program. These random samples have been confirmed by the National Health Research Institutes to be representative of the Taiwanese population. In this cohort data set, the patients' original identification numbers have been encrypted to protect their privacy, but the encrypting procedure was consistent, so that a linkage of the claims belonging to the same patient was feasible within the NHI database and can be followed continuously. The database with a large sample size provided an excellent opportunity to study the association between influenza infection, vaccination, and the risk of AF. The study was approved by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan.

Study population and control group

From January 1, 2000, to December 31, 2010, a total of 11,374 patients 20 years or older with the newly diagnosed AF were identified from the NHIRD using the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes (427.31).[15–17] The diagnostic accuracy of AF using *ICD-9-CM* codes in the NHIRD has been validated previously.[18,19] We defined the date of the first diagnosis of AF when each patient was enrolled to be the index date. On the same index date, 4 control patients (without AF) with matched age and sex were selected to be the control group (n = 45,496) for each study patient. We selected controls using risk set sampling,[20] which means that when a patient with AF was identified, 4 persons without AF who were still at risk at that point in time were selected from the data set. Thereafter, histories of influenza infection and vaccination 1 year before the enrollment were analyzed and compared between the study and control groups. The flowchart of the enrollment of study patients is given in Figure 1.

Information on important comorbid conditions of each individual was retrieved from the medical claims based on the *ICD-9-CM* codes. We defined patients with a certain disease only when it was a discharge diagnosis or repeatedly confirmed more than twice in outpatient department. The diagnostic accuracies of important comorbidities in the NHIRD, such as hypertension, diabetes mellitus, heart failure, myocardial infarction, hyperlipidemia, and chronic obstructive pulmonary disease, have been validated before.[21,22]

Statistical analysis

The data are presented as mean ± SD for normally distributed continuous variables and n(%) for categorical variables. The differences between continuous values were assessed using an unpaired 2-tailed *t* test for normally distributed continuous variables and Mann-Whitney rank-sum test for skewed variables. The χ^2 test was used for the comparisons of nominal variables. The risk of patients in developing AF was expressed as the odds ratio, which was analyzed using the logistic regression analysis. All statistical

significances were set at $P < .05$, and all statistical analyses were performed using SPSS 17.0 (SPSS Inc., IBM, Chicago).

Results

Patients' characteristics

The baseline characteristics of the patients with and without AF are summarized in Table 1. The mean age of the study population was 70.9 ± 13.4 years, and 55.7% of the patients were men. The age and sex were matched between the study and control groups. In regard to the comorbidities and frequencies of medical utilizations, patients with AF had more comorbidities and received imaging studies and visited outpatient department for upper respiratory tract and influenza infections more frequently than did patients without AF.

Influenza infection, vaccination, and risk of AF

Patients were divided into 4 groups on the basis of the status of influenza infection and vaccination. Patients who did not experience influenza infection nor receive vaccination 1 year before the index date were defined as the reference group. The risk of AF occurrence related to influenza infection and vaccination represented by odds ratios is shown in Table 2. After adjustment for age, sex, comorbidities, and medical utilizations, patients with influenza infection without vaccination were associated with a significantly higher risk of AF development with an adjusted odds ratio of 1.182 (95% confidence interval [CI] 1.014–1.378; $P = .032$) as compared with the reference group. The risk of AF was lower in patients receiving influenza vaccination without influenza infection (odds ratio 0.881; 95% CI 0.836–0.928; $P < .001$). In patients who have received influenza vaccination and experienced influenza infection, the risk of AF was similar to that in the reference group (odds ratio 1.136; 95% CI 0.929–1.389; $P = .214$).

A matching of Charlson Comorbidity Index[23] in addition to age and sex among patients with and without AF was performed, and the baseline characteristics of these 2 groups are summarized in Online Supplemental Table 1. The associations between influenza infection, vaccination, and AF were similar to the results of analyses performed in patients who were not matched for Charlson Comorbidity Index (Online Supplemental Table 2).

In patients receiving influenza vaccination and without influenza infection (n = 16,452), influenza vaccination was consistently associated with a lower risk of AF as compared with patients without influenza infection and vaccination (reference group) in different groups of patients stratified by age, sex, and important comorbidities (Figure 2).

Discussion

Main findings

In this nationwide case-control study that enrolled a total of 56,870 patients, we investigated the association between influenza infection, vaccination, and the risk of AF. The main findings were as follows: (1) influenza infection may increase the risk of AF, and the risk could be reduced through vaccination; And (2) influenza vaccination was consistently associated with a lower risk of AF in different groups of patients.

Table 1 Baseline characteristics of the patients with and without atrial fibrillation

Variables	Study group (with AF) (n = 11,374)	Control group (without AF) (n = 45,496)	P value
Age, years	70.9 ± 13.4	70.9 ± 13.4	0.955
Age ≥65 years old	8,305 (73.0)	33,206 (73.0)	0.947
Gender (male)	6,338 (55.7)	25,352 (55.7)	1.0
Medical history			
Hypertension	7,834 (68.9)	22,979 (50.5)	<0.001
Diabetes mellitus	3,325 (29.2)	10,155 (22.3)	<0.001
Congestive heart failure	3,802 (33.4)	4,142 (9.1)	<0.001
Myocardial infarction	639 (5.6)	823 (1.8)	<0.001
Peripheral vascular diseases	876 (7.7)	2,278 (5.0)	<0.001
COPD	3,923 (34.5)	9,974 (21.9)	<0.001
ESRD	922 (8.1)	1,722 (3.8)	<0.001
Ischemic stroke/TIA	2,432 (21.4)	5,871 (12.9)	<0.001
Hemorrhagic stroke	314 (2.8)	777 (1.7)	<0.001
GERD	548 (4.8)	1,609 (3.5)	<0.001
Sleep apnea	17 (0.1)	36 (0.1)	0.028
Cancer	2,432 (21.4)	8,082 (17.8)	<0.001
Dyslipidemia	2,766 (24.3)	9,509 (20.9)	<0.001
Dementia	850 (7.5)	2,548 (5.6)	<0.001
Major depression	787 (6.9)	2,370 (5.2)	<0.001
Autoimmune diseases	568 (5.0)	1,955 (4.3)	0.001
Liver cirrhosis	287 (2.5)	798 (1.8)	<0.001
Statin use	1,212 (10.7)	3,960 (8.7)	<0.001
Medical utilization (mean times 1 year before the enrollment)			
Computed tomography/MRI	0.36 ± 0.76	0.16 ± 0.51	<0.001
OPD visit for URTI	2.16 ± 4.33	1.70 ± 3.84	<0.001
Visit of influenza clinic	0.17 ± 1.17	0.14 ± 1.02	0.006
All-cause admission	0.80 ± 1.52	0.31 ± 0.96	<0.001

Table 2 Associations between influenza infection, vaccination, and atrial fibrillation

		Multivariate regression model*		
Influenza infection and vaccination	No. of patients	Odds ratio	95% CI	*P*
Neither (reference group)	38,353	1	—	—
Influenza infection only	1,369	1.182	1.014–1.378	.032
Vaccination only	16,452	0.881	0.836–0.928	<.001
Influenza infection and vaccination	696	1.136	0.929–1.389	.214

CI = confidence interval.

*Adjusted for age, sex, medical history, and medical utilization listed in Table 1.

Influenza infection and risk of AF

What is the possible mechanism behind the association between influenza infection and AF we observed in the present study? Several studies[4–6] have supported a close link between AF and inflammatory processes. An elevated serum CRP level was reported to be related to AF development, increased AF burden, and higher recurrence rate after catheter ablation and electrical cardioversion for AF.[24–27] Both TNF-α and IL-6 levels were significantly correlated with the left atrial diameter and duration of AF.[28–30] Previous studies[31–35] have demonstrated that a higher IL-6 level was associated with a higher risk of AF after coronary artery bypass graft surgery and a higher AF recurrence rate after cardioversion and radiofrequency catheter ablation. Furthermore, the autonomic nervous system played a vital role in the initiation and perpetuation of AF, and sympathovagal discharges could be a trigger for paroxysmal AF.[7,8]

During influenza infection, epithelial cells and leukocytes infected by influenza produced several proinflammatory cytokines, including IL-6 and TNF-α.[10] Serum CRP levels were also elevated in many inflammatory diseases including bacterial and, to a lesser degree, viral infections, such as influenza.[36] In response to influenza infection, the sympathetic nervous system was activated and modulated the immune system to increase proinflammatory cytokines, which further exacerbated influenza virus pathogenesis.[11,12] Taken together, influenza infection might increase the risk of AF through the activation of systemic inflammatory responses and increase of sympathetic tone. However, the precise mechanisms responsible for the link between

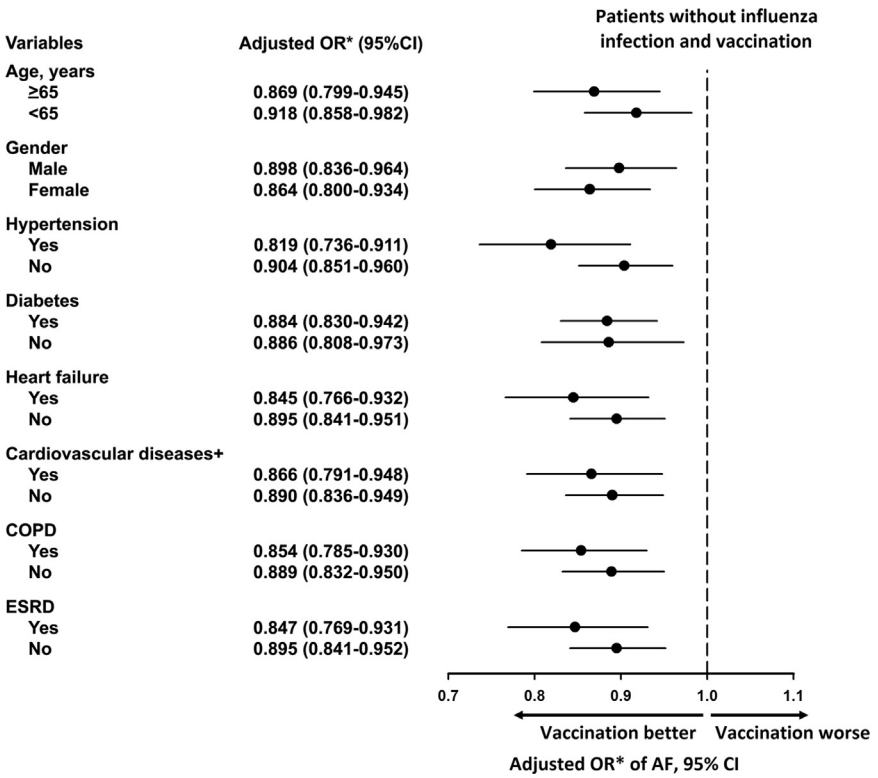

Figure 2 Forest plot describing subgroup analysis of the association between vaccination and AF. For patients receiving influenza vaccination and without influenza infection (n = 16,452), influenza vaccination was consistently associated with a lower risk of AF as compared with patients without influenza infection and vaccination (reference group) in different groups of patients stratified by age, sex, and important comorbidities. AF = atrial fibrillation; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ESRD = end-stage renal disease; OR = odds ratio. *Adjusted for age, sex, medical history, and medical utilization listed in Table 1. +Cardiovascular diseases included peripheral vascular diseases, myocardial infarction, and ischemic stroke/transient ischemic attack.

influenza infection and AF remain unclear, and further studies are necessary to investigate this issue.

Clinical applications

The occurrence of cardiac arrhythmias after influenza infection, including atrioventricular block,[37] cardiac conduction system affection,[38] atrial arrhythmia,[39] and ventricular arrhythmia,[40] was reported in previous case reports. The present study represents the first population-based study investigating the association between influenza infection, vaccination, and occurrence of AF. According to the findings presented here, the possibility of AF should be kept in mind when patients with influenza infection complained of palpitation or experienced ischemic stroke. In addition, influenza vaccination may be a useful way to reduce the AF burden associated with influenza infection, and high-risk patients should be encouraged to receive influenza vaccination annually.

Study limitations

There are several limitations of the present study. First, personal information such as smoking habit, physical activity, and body mass index were not available from this registry database. In addition, echocardiographic parameters, such as left atrial dimension and left ventricular ejection fraction, were absent. Therefore, we were not able to control well for all potential confounders, although we have tried to adjust for important comorbidities in the Cox regression model. Second, the diagnosis of AF was based on the diagnostic code registered by the physicians responsible for the treatments of patients and was not further checked externally. However, the diagnostic accuracy of AF in the NHIRD has been validated before.[18,19] Third, influenza infection was diagnosed using *ICD-9* codes with concomitant use of antiviral agents and was not further confirmed on the basis of the results of viral culture with throat swab. The diagnostic accuracy of influenza infection cannot be fully ascertained. Lastly, while we reported the significant association between AF and influenza infection, these results were derived from an observational database. Therefore, we were not able to conclude whether influenza infection was the direct cause of the increased risk of AF, and only a prospective and randomized trial can answer the question. However, the observed lower risk of AF in patients receiving influenza vaccination may partly support the hypothesis that influenza infection was an important risk factor for AF.

Conclusion

In this observational study, influenza infection was significantly associated with the development of AF, with an 18% increase in the risk, which could be reduced through influenza vaccination. A further prospective and large-scale trial is necessary to confirm the findings of the present study.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.hrthm.2016.01.026

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