ACEI and ARB did not Reduce the Incidence of Dementia in Patients with Atrial Fibrillation: A Nationwide Cohort Study

Min-Tsun Liao,[1] Lian-Yu Lin,[2]* Yao-Hsu Yang,[3,4] Tin-Tse Lin,[2] Jiunn-Lee Lin,[2] Pau-Chung Chen[4] and Chia-Ti Tsai[2]*

Purpose: Atrial fibrillation (AF) is associated with increased risk of thromboembolism, and is also a predisposing factor to dementia. Our investigation was a retrospective observational study to evaluate whether the usage of angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) could reduce the incidence of dementia in patients with AF.

Methods: A total of 5221 patients over 20 years of age who had a history of AF as noted in ambulatory and inpatient claims data were enrolled from the National Health Insurance Research Database of Taiwan in 1997 and 1998. Patients with ACEI or ARB were designated as group 1 (4343 patients), and patients without ACEI or ARB were designated as group 2 (878 patients).

Results: During a follow-up of 5.90 ± 3.39 years, 135 patients of group 1 (3.1%) and 25 of group 2 (2.8%) developed new-onset dementia. Group 1 and group 2 had similar proportions of new-onset dementia (p = 0.75). The Kaplan-Meier curve demonstrated that patients with ACEI or ARB were not associated with a lower incidence of dementia during the follow-up period (log rank p = 0.91). Cox-regression analysis also showed that usage of ACEI or ARB was not associated with a lower risk of new-onset dementia after adjustment for gender and comorbidities. (Hazard ratio = 0.942, 95% confidence interval 0.589~1.506, and p = 0.80).

Conclusions: ACEI or ARB may be ineffective in reducing the incidence of dementia in patients with AF.

Key Words: Angiotensin-converting-enzyme inhibitor • Angiotensin II receptor blocker • Atrial fibrillation • Dementia

INTRODUCTION

Atrial fibrillation (AF) is the most commonly occurring arrhythmia in older patients, occurring in 1-2% of the general population.[1] It is also associated with a high risk of ischemic stroke and thromboembolism; it contributes a 5-fold risk of stroke, and is responsible for approximately 15% of all strokes.[2] The risk of cerebrovascular thromboemboli might predispose a patient to cognitive dysfunction and dementia. Recent study has demonstrated that the risk of dementia increases after stroke.[3] Some meta-analysis studies also have revealed that AF is independently associated with an increased risk of dementia.[4,5] Interestingly, dementia or cognitive dysfunction have similar underlying risk factors as those of AF, including age, hypertension and diabetes. The prevalence of dementia varies widely in different countries, from 0.3% to 6.3%.[6] Around 24.3 million people had dementia in 2001

Received: May 15, 2013 Accepted: June 5, 2013
[1]Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital Hsin-Chu Branch, Hsinchu; [2]Division of Cardiology, Department of Internal Medicine, National Taiwan University Hospital, Taipei; [3]Department for Traditional Chinese Medicine, Chang Gung Memorial Hospital Chia-Yi; [4]Institute of Occupational Medicine and Industrial Hygiene, National Taiwan University College of Public Health, Taipei, Taiwan.
Address correspondence and reprint requests to: Dr. Chia-Ti Tsai, Division of Cardiology, Department of Internal Medicine, National Taiwan University College of Medicine and Hospital, No. 7, Chung-Shan South Road, Taipei 100, Taiwan. Tel: 886-2-2312-3456 ext. 63588; Fax: 886-2-8231-7099; E-mail: fang31@ms39.hinet.net; cttsai1999@gmail.com
* These authors contributed equally to the work.

and the number was expected to double every 20 years.[7]

Guidelines for AF in both ESC 2010[8] and ACC/AHA/ESC 2006[9] also recommended that angiotensin converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) should be considered for primary and secondary prevention of AF in patients with hypertension. A meta-analysis study supports the prevention of AF by renin-angiotensin system inhibition.[10] Recently, renin-angiotensin system blockades have been shown to reduce the incidence and progression of dementia in patients with cerebrovascular disease.[11] So far, there has been no study that addresses how to treat dementia in patients with AF. The aim of the present undertaking was a retrospective observational study to investigate whether using ACEI or ARB could reduce the incidence of dementia in patients with AF.

MATERIALS AND METHODS

Registry data sources

A universal national health insurance (NHI) program was first implemented in Taiwan almost 20 years ago, and has been ongoing since 1995. Currently, some 96% of the total Taiwanese population has enrolled in the NHI program.[12] By the end of 1996, the Bureau of NHI (BNHI) had contracted with 97% of all hospitals and clinics throughout the nation.[13] The BNHI accumulates all administrative and claims data for Taiwan. To provide access to this accumulated information, the National Health Research Institute (NHRI) cooperates with the BNHI to establish and maintain the NHI research database. The NHRI safeguards the privacy and confidentiality of all beneficiaries and transfers the health insurance data to health researchers after ethical approval has been obtained. To ensure the accuracy of the claim files, the BNHI performs expert review on a random sample of every 50-100 ambulatory and inpatient claims quarterly, and any false report of diagnosis can result in a severe penalty from the BNHI.[14,15] Data for gender, birth date, medications, and diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification were retrieved for the analyses performed in this study.

Study population and outcomes

For the current analysis, we used a systemic sampling database from 1997 and 1998 with a total of 1,000,000 subjects in the national registry database. By using ambulatory and inpatients claim data, we included subjects with atrial fibrillation who were all over 20 years of age. The study also included patients with normal cognitive function at baseline who had not suffered an acute stroke. Ultimately, a total of 5221 subjects were included in the final analyses.

Comorbidity and concomitant medication

In our study population, we searched the database for patients who had hypertension (HTN), diabetes mellitus (DM), hyperlipidemia, congestive heart failure (CHF), chronic kidney disease (CKD), valvular heart disease (VHD) or cardiovascular diseases including coronary artery disease (CAD), myocardial infarction (MI), peripheral arterial disease (PAD), transient ischemic accident (TIA) or ischemic stroke. To ascertain the study endpoint, we reviewed the inpatients' claim data to find if they had dementia after diagnosis of atrial fibrillation.

Statistical analysis

Basic characteristics were expressed as percentage. The hazard ratio for the risk of dementia was derived from a multivariable Cox regression analysis and was adjusted for all possible baseline confounders or covariates, such as gender, age (> 50 years old), HTN, DM, hyperlipidemia, history of MI, PAD, CAD, CKD, VHD, CHF and usage of ACEI or ARB. The dementia-free survival time was defined as the time from the day of enrollment to the occurrence of a diagnosis of dementia. If an event (dementia) did not occur, the case was regarded as censorship at the end of the study. Kaplan-Meier curves with statistical significance examination using the long-rank test plotted to show the event-free survival trend between subjects with and without ACEI/ARB. All analyses were performed with SPSS 18.0 for Windows 7 (SPSS Inc. Chicago, IL, USA). For all analyses, a 2-tailed p value $< .05$ was considered statistically significant.

RESULTS

The basic demography was summarized in Table 1. A total of 5221 patients (2864 women and 2357 men) were included in the final analyses, including 4343

patients with ACEI or ARB who were defined as group 1 and 878 patients without ACEI or ARB who were defined as group 2. During a follow-up of 5.90 ± 3.39 years, group 1 and 2 had 135 (3.1%) and 25 (2.8%) patients experiencing new-onset dementia, respectively, which were not significantly different (p = 0.75). The Kaplan-Meier curve also demonstrated that patients with ACEI or ARB were not associated with a lower incidence of dementia during the follow-up period (log rank p = 0.91, Figure 1).

However, group 1 and group 2 were not balanced in terms of various cardiovascular risk factors. Patients with ACEI or ARB tended to be elderly, and had a higher percentage of comorbid cardiovascular conditions including hypertension, diabetes mellitus, myocardial infarction, hyperlipidemia, congestive heart failure, previous ischemic stroke, and chronic kidney disease (Table 1). Therefore, these factors should be adjusted in analyzing the effect of ACEI/ARB on the incidence of dementia.

We used Cox-regression analysis to evaluate the effect of ACEI/ARB on the incidence of dementia, while adjusting for the possible aforementioned confounding factors. Cox-regression analysis still showed that usage of ACEI/ARB was not associated with a lower risk of developing dementia after adjusting all possible confounders (hazard ratio = 0.942, 95% CI 0.589~1.506, and p = 0.80). But there are some generally accepted predictors for dementia such as gender, age > 50 years old, CHF and hyperlipidemia.

Table 1. Basic demography of the study population

Clinical characteristics	Group 1 N = 4343	Group 2 N = 878	p valve
Age, y	64 ± 11	58 ± 13	< 0.001
Gender, F/M	2375 (54.7%)	489 (55.7%)	0.60
Hypertension	3756 (86.5%)	336 (38.3%)	< 0.001
Diabetes mellitus	1394 (32.1%)	142 (16.2%)	< 0.001
Myocardial infarction	126 (2.9%)	5 (0.6%)	< 0.001
Hyperlipidemia	1499 (34.5%)	153 (17.4%)	< 0.001
CHF	2049 (47.2%)	161 (18.3%)	< 0.001
Stroke	946 (21.8%)	124 (14.1%)	< 0.001
TIA	459 (10.6%)	62 (7.1%)	0.001
TIA or stroke	1297 (29.9%)	163 (18.6%)	< 0.001
PAD	1153 (26.5%)	149 (17.0%)	< 0.001
CAD	2851 (65.6%)	378 (43.1%)	< 0.001
CKD	436 (10.0%)	22 (2.5%)	< 0.001
VHD	513 (11.8%)	79 (9.0%)	0.02
New Dementia, (%)	135 (3.1%)	25 (2.8%)	0.75

CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; PAD, peripheral artery disease; TIA, transient ischemic attack; VHD, valvular heart disease.

DISCUSSION

AF has been proven to be associated with dementia,[16,17] but so far there has been no study or trial to investigate the effect of ACEI and ARB to prevent dementia in patients with AF. To the best of our knowledge, this was the first large-scale nationwide study which examined the effect of the ACEI or ARB on new onset dementia in patients with AF. After adjustment for various potential risk factors, our results indicated a similar risk of new onset dementia in AF patients either with or without ACEI or ARB treatment.

AF is associated with increased rates of stroke and thromboembolic events, and results in long-term disability or death. The thromboembolic events, irrespective of major stroke or asymptomatic embolism, may be the causes of dementia and cognitive dysfunction. Recent data support a causal link between AF and dementia, which has revealed that effective rhythm-control therapy by means of radiofrequency catheter ablation

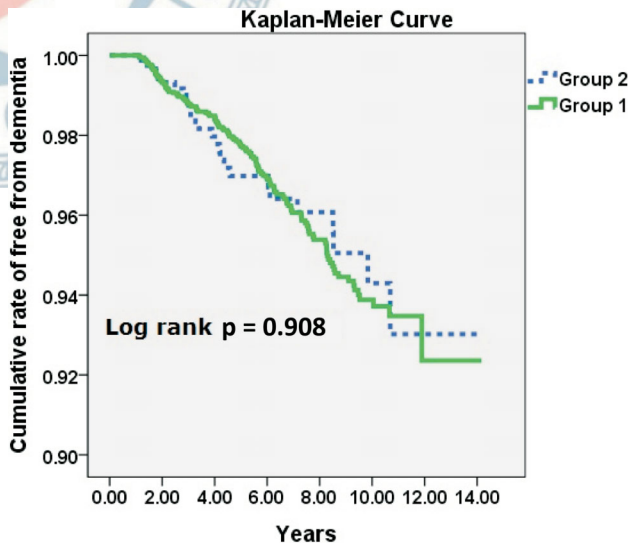

Figure 1. *Kaplan-Meier curves of cumulative rate of free from dementia. Solid line indicates patients taking angiotensin-converting-enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) (Group 1); Dotted line indicates patients not taking ACEI or ARB (Group 2).*

might reverse the risk of dementia associated with AF.[16] A prior small observational study also suggested that asymptomatic embolic events might contribute to cognitive impairment in AF patients even in the absence of a manifest stroke.[17] On the other hand, the relationship between AF and dementia may not be cause and effect relationship. Both may be the result of a common underlying systemic vascular disease such as atherosclerosis. Consequently, further investigation is warranted to demonstrate the causal link between AF and increased risk of dementia.

Renin-angiotensin system blockades could prevent the development of AF as primary prevention, particularly in those patients with hypertension.[18] It has also been proven that renin-angiotensin system blockades can also reduce the incidence and progression of dementia or cognitive dysfunction in non-AF patients.[11,19,20] Therefore, the benefit of using renin-angiotensin system blockades for patients with AF may be two-sided: either decrease AF burden or prevent dementia or cognitive dysfunction. Unfortunately, our study revealed the similar incidence of dementia between AF patients with and without renin-angiotensin system blockades. Further randomized control trials may be needed to substantiate our finding.

STUDY STRENGTH AND LIMITATIONS

The strengths of this study included its population-based, nationwide study design that captured all validated cases of AF over a mean 5-year period with a reasonably high case number. All comorbidities and medical interventions were dutifully recorded under procedures within the national health insurance policy. However, there were several limitations in our study. First, it is difficult to reach a reliable diagnosis of dementia in a short period of time (mean 5.90 $\pm$ 3.39 years). Second, the claim data from National Health Insurance Research Database of Taiwan may result in potential disease classification bias. Third, the type of AF cannot be checked from the database, such as paroxysmal, persistent, longstanding persistent or permanent. Some studies have shown that the duration of AF is an important risk factor for intra-cardiac thrombi[21] and possibly dementia. Fourth, although the most important risk factors for dementia such as age, hypertension, and comorbid conditions were controlled, there was a lack of data for other confounders such as obesity, smoking, alcohol consumption, family history, lifestyle, and diet.

CONCLUSIONS

In summary, this study showed that the risk of new-onset dementia was similar between AF patients either with or without ACEI/ARB treatment. Further randomized trials may be needed to prove this finding.

DISCLOSURES

None.

REFERENCES

1. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA* 2001;285:2370-5.
2. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994;154:1449-57.
3. Altieri M, Di Piero V, Pasquini M, et al. Delayed poststroke dementia: a 4-year follow-up study. *Neurology* 2004;62:2193-7.
4. Santangeli P, Di Biase L, Bai R, et al. Atrial fibrillation and the risk of incident dementia: a meta-analysis. *Heart Rhythm* 2012;9:1761-8.
5. Kwok CS, Loke YK, Hale R, et al. Atrial fibrillation and incidence of dementia: a systematic review and meta-analysis. *Neurology* 2011;76:914-22.
6. Llibre Rodriguez JJ, Ferri CP, Acosta D, et al. Prevalence of dementia in Latin America, India, and China: a population-based cross-sectional survey. *Lancet* 2008;372:464-74.
7. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. *Lancet* 2005;366:2112-7.
8. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Eur Heart J* 2010;31:2369-429.
9. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation--executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice

Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol* 2006;48:854-906.
10. Schneider MP, Hua TA, Bohm M, et al. Prevention of atrial fibrillation by Renin-Angiotensin system inhibition - a meta-analysis. *J Am Coll Cardiol* 2010;55:2299-307.
11. Tzourio C, Anderson C, Chapman N, et al. Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease. *Arch Intern Med* 2003;163:1069-75.
12. Lu JF, Hsiao WC. Does universal health insurance make health care unaffordable? Lessons from Taiwan. *Health Aff (Millwood)* 2003;22:77-88.
13. Chiang TL. Taiwan's 1995 health care reform. *Health Policy* 1997;39:225-39.
14. Tseng CH. Mortality and causes of death in a national sample of diabetic patients in Taiwan. *Care Diabetes* 2004;27:1605-9.
15. Chen HF, Ho CA, Li CY. Age and sex may significantly interact with diabetes on the risks of lower-extremity amputation and peripheral revascularization procedures: evidence from a cohort of a half-million diabetic patients. *Diabetes Care* 2006;29:2409-14.
16. Bunch TJ, Crandall BG, Weiss JP, et al. Patients treated with catheter ablation for atrial fibrillation have long-term rates of death, stroke, and dementia similar to patients without atrial fibrillation. *J Cardiovasc Electrophysiol* 2011;22:839-45.
17. Knecht S, Oelschlager C, Duning T, et al. Atrial fibrillation in stroke-free patients is associated with memory impairment and hippocampal atrophy. *Eur Heart J* 2008;29:2125-32.
18. Larstorp AC, Ariansen I, Gjesdal K, et al. Association of pulse pressure with new-onset atrial fibrillation in patients with hypertension and left ventricular hypertrophy: the Losartan Intervention For Endpoint (LIFE) reduction in hypertension study. *Hypertension* 2012;60:347-53.
19. Furiya Y, Ryo M, Kawahara M, et al. Renin-angiotensin system blockers affect cognitive decline and serum adipocytokines in Alzheimer's disease. *Alzheimers Dement* 2012.
20. Fournier A, Oprisiu-Fournier R, Serot JM, et al. Prevention of dementia by antihypertensive drugs: how AT1-receptor-blockers and dihydropyridines better prevent dementia in hypertensive patients than thiazides and ACE-inhibitors. *Expert Rev Neurother* 2009;9:1413-31.
21. Chien KL, Su TC, Hsu HC, et al. Constructing the prediction model for the risk of stroke in a Chinese population: report from a cohort study in Taiwan. *Stroke* 2010;41:1858-64.