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 Chen4 and Chia-Ti Tsai2

**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. 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. 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. Some meta-analysis studies also have revealed that AF is independently associated with an increased risk of dementia. 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%. Around 24.3 million people had dementia in 2001.
and the number was expected to double every 20 years.\textsuperscript{7}

Guidelines for AF in both ESC 2010\textsuperscript{8} and ACC/AHA/ESC 2006\textsuperscript{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.\textsuperscript{10} Recently, renin-angiotensin system blockades have been shown to reduce the incidence and progression of dementia in patients with cerebrovascular disease.\textsuperscript{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.\textsuperscript{12} By the end of 1996, the Bureau of NHI (BNHI) had contracted with 97\% of all hospitals and clinics throughout the nation.\textsuperscript{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.\textsuperscript{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 event (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 log-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.

**DISCUSSION**

AF has been proven to be associated with dementia, 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

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

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

**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. 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. 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. 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. 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 ± 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 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


