Available online at www.sciencedirect.com

ScienceDirect

Journal of the Chinese Medical Association 79 (2016) 470−476

www.jcma-online.com

Original Article

Prediction of vascular dementia and Alzheimer's disease in patients with atrial fibrillation or atrial flutter using $CHADS_2$ score

Ruey-Hsing Chou [a,b], Chun-Chih Chiu [a,b], Chin-Chou Huang [a,b,c], Wan-Leong Chan [a,d], Po-Hsun Huang [a,b,e], Yu-Chun Chen [f,g], Tzeng-Ji Chen [f,h], Chia-Min Chung [i], Shing-Jong Lin [a,b,c,e], Jaw-Wen Chen [a,b,c,j], Hsin-Bang Leu [a,b,d,e,*]

[a] *Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[b] *Cardiovascular Research Center, National Yang-Ming University, Taipei, Taiwan, ROC*
[c] *Department of Medical Research and Education, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[d] *Healthcare and Management Center, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[e] *Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan, ROC*
[f] *Department of Family Medicine, Taipei Veterans General Hospital, Taipei, Taiwan, ROC*
[g] *Department of Medical Informatics, University of Heidelberg, Heidelberg, Germany*
[h] *Institute of Hospital and Health Care Administration, National Yang-Ming University, Taipei, Taiwan, ROC*
[i] *Institute of Biomedical Sciences, Academia Sinica, Taipei, Taiwan, ROC*
[j] *Institute of Pharmacology, National Yang-Ming University, Taipei, Taiwan, ROC*

Received October 20, 2015; accepted February 2, 2016

Abstract

Background: Atrial fibrillation (AF) is associated with an increased risk of dementia. However, limited data are available on the predictors of dementia in patients with AF. This study aimed to evaluate whether the $CHADS_2$ score could be a useful tool for risk stratification with regard to dementia occurrence among patients with AF.
Methods: AF patients were identified from the National Health Insurance sampling database, which has accumulated a total of 1,000,000 participants since 2000. After excluding patients diagnosed with dementia prior to the index day of enrollment, $CHADS_2$ score was measured to investigate its association with the occurrence of dementia, including vascular dementia and Alzheimer's disease.
Results: During the mean follow-up period of 3.71 ± 2.78 years, 1135 dementia cases (7.36%) were identified, including 241 cases of vascular dementia and 894 cases of Alzheimer's disease. In multivariate analysis, an increase of 1 point in the CHADS2 score was independently associated with a 54% increase in the risk of vascular dementia (hazard ratio = 1.54; 95% confidence interval, 1.41−1.69; $p < 0.001$) and a 40% increase in Alzheimer's disease (hazard ratio = 1.40; 95% confidence interval, 1.34−1.46; $p < 0.001$).
Conclusion: $CHADS_2$ score is a useful predictor for the development of vascular dementia as well as Alzheimer's disease in patients with AF.
Copyright © 2016, the Chinese Medical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Alzheimer's disease; atrial fibrillation; CHADS2 score; dementia; stroke

1. Introduction

Evidence increasingly suggests that atrial fibrillation (AF) is associated with late-life dementia.[1] This strong association is not only seen in vascular dementia, but also in Alzheimer's disease (AD).[2] It has been reported that AF may be associated with higher risk of cognitive function impairment and may

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

* Corresponding author. Dr. Hsin-Bang Leu, Healthcare and Management Center, Division of Cardiology, Department of Medicine, Taipei Veterans General Hospital, 201, Section 2, Shih-Pai Road, Taipei 112, Taiwan, ROC.
E-mail addresses: hbleu@vghtpe.gov.tw, hsinbangleu@gmail.com (H.-B. Leu).

http://dx.doi.org/10.1016/j.jcma.2016.02.007
1726-4901/Copyright © 2016, the Chinese Medical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

carry a higher risk of dementia development. One important explanation is the increased incidence of stroke. Ott et al[3] have demonstrated that even among AF patients without stroke, AF is still associated with dementia and AD. Both vascular dementia and AD had been reported to be associated with AF. $CHADS_2$ has been reported to be of use for risk stratification regarding stroke recurrence among patients with AF[4] and has also been reported to predict AF recurrence after ablation and predict AF complications among AF patients.[5,6] However, information about the use of $CHADS_2$ score to predict dementia, including vascular dementia and AD, is limited. Therefore, we conducted a large-scale, nationwide, population-based cohort study to investigate the correlation between the $CHADS_2$ score and the future risk of vascular dementia or AD, and whether it could be a useful tool to stratify risk in AF patients.

2. Methods

2.1. Study population and data source

The National Health Insurance program has enrolled nearly all the inhabitants of Taiwan since 1995. As described in our previous study,[7,8] the National Health Research Institute (NHRI) in Miaoli, Taiwan, manages the complete National Health Insurance claims database, and makes datasets available to applicants for medical research purposes. In each dataset, the patient's original identification number has been encrypted to protect privacy, using a consistent encrypting procedure, thus allowing linkage of claims belonging to the same patient within the NHRI database.

Patients with AF or atrial flutter were identified according to ICD coding (*International Classification of Diseases, 9th Revision, Clinical Modification* code 427.31, 427.32) from a cohort dataset of 1 million individuals sampled from the NHRI database between January 1, 2000 and December 31, 2009. Diagnosis of AF was identified using coding by qualified cardiologists for the purpose of insurance claims. The date of AF occurrence was set as the date when the diagnosis first presented in the dataset. To clearly demonstrate the relationship between AF and occurrence of dementia, AF with previous dementia diagnosis prior to the index date of enrollment were excluded in this study. A similar definition for AF has been described in our previous works.[7–10]

2.2. Identification of dementia

To investigate the association between AF and dementia, vascular dementia and AD were analyzed separately. The diagnosis of dementia was identified using coding by a qualified neurologist, either presented once in the diagnosis of hospitalization or presented at least two times in outpatient clinic visits. The ultimate diagnosis should be correct due to the insurance claim purposes. Vascular dementia was defined as the presence of arteriosclerotic dementia (ICD 9: 290.4, 290.40, 290.41, 290.42, 290.43), following the diagnosis of newly developed stroke (ICD 9: 433.xx–438.xx), and undergoing at least one image study (computed tomography, brain magnetic resonance imaging) after enrollment. AD was identified with the ICD code of Alzheimer's disease (331.0). In addition, senile dementia (290.0, 290.2, 290.20, 290.21, 290.3) without stroke or other significant secondary cause[11–13] of cognitive impairment was also identified as AD in this study. Similar methods for the identification of AD were applied in our previous works.[8,10] All patients were followed up until December 31, 2009, or until the presence of either type of dementia was noted.

2.3. $CHADS_2$ score and study variables

In addition to age and sex, we identified the following comorbidities for each patient upon initiation of the study: hypertension (401.xx–405.xx), diabetes mellitus (250.xx), coronary artery disease (410.xx–414.xx), stroke (430.xx–438.xx), chronic kidney disease (580.xx–587.xx), congestive heart failure (428.xx), peripheral artery disease (440.xx–444.xx), chronic obstructive pulmonary disease (490.xx–496.xx), and valvular heart disease (424.xx). The ICD codes of the comorbidities were summarized in Table S1. Variables that are components of the $CHADS_2$ score were retrieved. The $CHADS_2$ score is a risk stratification score that ranges from 0 to 6 and is calculated as follows: congestive heart failure (1 point), hypertension (1 point), age $\geq$ 75 years (1 point), diabetes mellitus (1 point), and stroke (2 points). The $CHADS_2$ score was calculated for each participant at study entry.[4]

Concomitant medication usage (aspirin, ticlopidine, clopidogrel, warfarin, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, thiazide, statins) was identified and classified according to the National Drug Code and the Anatomic Therapeutic Chemical code, an internationally accepted drug classification system coordinated by the World Health Organization Collaborating Center for Drug Statistics Methodology. Patients must have received a prescription for at least 90 days during the observation period in order to be identified as a medical user. This study was exempt from full review by the Institutional Review Board of Taipei Veterans General Hospital, Taipei, Taiwan, because the selected dataset consisted of deidentified secondary data released to the public for research purposes.

2.4. Statistical analysis

We used Microsoft SQL Server 2005 (Microsoft Corporation, Redmond, Wash) to manage and compute the data. Statistical analysis was performed using SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA). Ordinal and categorical data were expressed as the frequency (%), and continuous data were expressed as mean ± standard deviation. The categorical data were compared between the two cohorts with Chi-square test and Yates' correction or Fisher's exact test. Continuous data among the different groups of patients were compared using unpaired Student *t* tests. Survival curves were assessed by the Kaplan–Meier method, and survival among groups was

compared by the log-rank test. The area under the ROC curve (AUC), or C-statistics, was used as a measure of the predictive accuracy of $CHADS_2$ score. The criterion value of the scoring system was determined by the Youden index, sensitivity + specificity −1. To assess the independent effects of the CHADS2 score, we conducted Cox proportional hazard regression models simultaneously adjusting for sex and comorbidities not included in the calculation of the $CHADS_2$ score (coronary artery disease, chronic kidney disease), as well as concomitant medication use (aspirin, ticlopidine, clopidogrel, warfarin, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, thiazide, statins) in the model. A two-sided p value < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Patient characteristics

A total of 15,430 patients with AF or atrial flutter without previously diagnosed dementia were enrolled in this study. The baseline characteristics of study participants are shown in Table 1. The incidence of hypertension, diabetes, history of stroke, and congestive heart failure were 77%, 36.3%, 38.2%, and 42.7%, respectively, and the mean $CHADS_2$ score was 2.73 ± 1.63. During the mean follow-up of 3.71 ± 2.78 years, 1135 cases of dementia (7.36%) were diagnosed, with 241 cases and 894 cases of vascular dementia and AD, respectively (Fig. 1). AF patients with dementia were older (77.37 ± 8.01 vs. 69.54 ± 13.1%, $p < 0.001$) and had a higher incidence of hypertension, coronary artery disease, history of stroke/transient ischemic attack (TIA), and chronic kidney disease (Table 2). In addition to having more comorbidities, patients with dementia were also taking more medications including antiplatelet agents, antihypertensive agents, and statins. Compared to patients developing AD, a higher percentage of AF patients developing vascular dementia were using antiplatelet agents, anticoagulant agents, and statins, and had higher $CHADS_2$ scores (3.6 ± 1.4 vs. 3.39 ± 1.45, $p = 0.043$; Table 3).

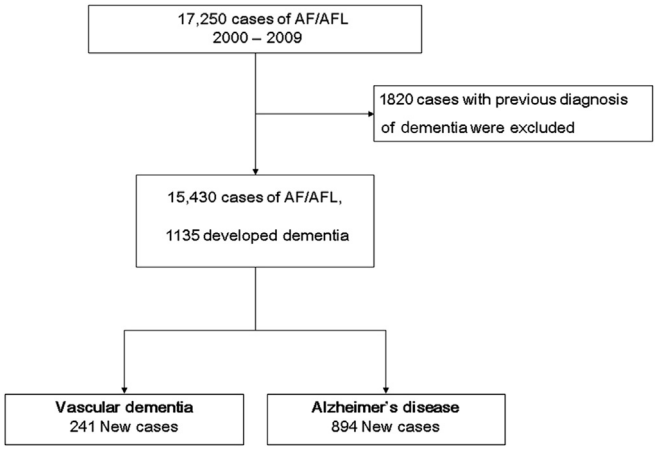

Fig. 1. Flowchart of patient enrollment. AF = atrial fibrillation; AFL = atrial flutter.

Table 1
Baseline characteristics of patients with atrial fibrillation.

	n = 15,430
Age (y)	70.11 ± 12.96
Male	8744 (56.7)
Medical history	
Hypertension	11,877 (77.0)
Diabetes mellitus	5595 (36.3)
Congestive heart failure	6585 (42.7)
Coronary artery disease	9827 (63.7)
Previous stroke/TIA	5898 (38.2)
Peripheral artery disease	2241 (14.5)
Chronic kidney disease	3522 (22.8)
COPD	8748 (56.7)
Valvular heart disease	3627 (23.5)
Medications	
Aspirin	7082 (45.9)
Licodin	556 (3.6)
Clopidogrel	1665 (10.8)
Warfarin	2529 (16.4)
ACEI	3756 (24.3)
ARB	5220 (33.9)
CCB	7881 (51.1)
Thiazide	3813 (24.7)
Statins	2504 (16.2)
$CHADS_2$ score*	2.73 ± 1.63

Data are presented as n (%) or mean ± standard deviation.
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack.

Table 2
Baseline characteristics of AF patients with and without dementia.

	With dementia (n = 1135)	Without dementia (n = 14,295)	p
Age (y)[a]	77.37 ± 8.01	69.54 ± 13.1	<0.001
Male (%)	558 (49.2)	8186 (57.3)	<0.001
Medical history			
Hypertension	979 (86.3)	10,898 (76.2)	<0.001
Diabetes mellitus	459 (40.4)	5136 (35.9)	0.002
Congestive heart failure	501 (44.1)	6084 (42.6)	0.300
Coronary artery disease	793 (69.9)	9034 (63.2)	<0.001
Previous stroke/TIA	609 (53.7)	5289 (37.0)	<0.001
Peripheral artery disease	185 (16.3)	2056 (14.4)	0.078
Chronic kidney disease	300 (26.4)	3222 (22.5)	0.003
COPD	664 (58.5)	8084 (56.6)	0.202
Valvular heart disease	249 (21.9)	3378 (23.6)	0.196
Medications			
Aspirin	912 (62.0)	6379 (44.6)	<0.001
Licodin	97 (6.6)	480 (3.4)	<0.001
Clopidogrel,	197 (13.4)	1506 (10.5)	0.001
Warfarin	262 (17.8)	2324 (16.3)	0.123
ACEI	534 (36.3)	3342 (23.4)	<0.001
ARB	542 (36.9)	4796 (33.6)	0.010
CCB	959 (65.2)	7141 (50.0)	<0.001
Thiazide	467 (31.8)	3436 (24.0)	<0.001
Statins	195 (13.3)	2345 (16.4)	0.002
$CHADS_2$ score	3.43 ± 1.44	2.68 ± 1.63	<0.001

Data are presented as n (%) or mean ± standard deviation.
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack.

Table 3
Baseline characteristics of patients with vascular dementia and Alzheimer's disease.

	Vascular dementia (n = 241)	Alzheimer's disease (n = 894)	p
Age (y)[a]	76.95 ± 7.98	77.49 ± 8.02	0.351
Male (%)	120 (49.8)	438 (49.0)	0.826
Medical history			
Hypertension	205 (85.1)	774 (86.6)	0.544
Diabetes mellitus	100 (41.5)	359 (40.2)	0.707
Congestive heart failure	101 (41.9)	400 (44.7)	0.432
Coronary artery disease	166 (68.9)	627 (70.1)	0.706
Previous stroke/TIA	153 (63.5)	456 (51.0)	0.001
Peripheral artery disease	38 (15.8)	147 (16.4)	0.801
Chronic kidney disease	70 (29.0)	230 (25.7)	0.300
COPD	131 (54.4)	533 (59.6)	0.141
Valvular heart disease	55 (22.8)	194 (21.7)	0.709
Medications			
Aspirin	174 (72.2)	529 (59.2)	<0.001
Licodin	23 (9.5)	53 (5.9)	0.046
Clopidogrel	51 (21.2)	108 (12.1)	<0.001
Warfarin	59 (24.5)	146 (16.3)	0.004
ACEI	89 (36.9)	325 (36.4)	0.869
ARB	100 (41.5)	324 (36.2)	0.135
CCB	148 (61.4)	592 (66.2)	0.164
Thiazide	80 (33.2)	297 (33.2)	0.994
Statins	48 (19.9)	111 (12.4)	0.003
$CHADS_2$ score[a]	3.60 ± 1.40	3.39 ± 1.45	0.043

Data are presented as n (%) or mean ± standard deviation.
ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CCB = calcium channel blocker; COPD = chronic obstructive pulmonary disease; TIA = transient ischemic attack.

3.2. $CHADS_2$ score and dementia

In order to investigate the correlation between risk of developing dementia and $CHADS_2$ score among AF patients, the incidence of dementia development was analyzed according to an increasing $CHADS_2$ score. Fig. 2 shows the incidence of developing dementia to be significantly associated with $CHADS_2$ score. The incidence of dementia was 1.98% per 100 person-years in the AF population. As the $CHADS_2$ score increased, the incidence of dementia augmented gradually, which was up to 4.86% for patients with a 6-point $CHADS_2$ score (Table 4).

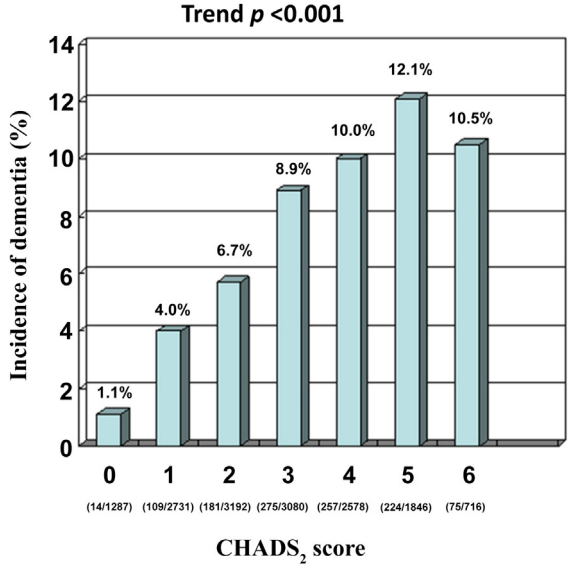

Fig. 2. The incidence of dementia continuously correlates with $CHADS_2$ scores among patients with atrial fibrillation (AF).

Using Kaplan–Meier analyses has clearly shown that the risk of developing dementia is associated with increasing $CHADS_2$ score over time (Fig. 3), regardless of whether patients developed vascular dementia (log rank $p < 0.001$) or AD (log rank $p < 0.001$), indicating that increasing $CHADS_2$ score correlated with the risk of developing dementia in AF patients.

Table 5 shows the C-statistics for the $CHADS_2$ score in predicting the incidence of dementia and its subtypes. As a predictor for dementia, $CHADS_2$ score showed acceptable sensitivity, but with relatively low specificity. Unsurprisingly, the discriminatory performance of $CHADS_2$ score was better in predicting vascular dementia than predicting AD.

3.3. Hazard analysis of individual factors of CHADS2 score

The Cox proportional hazard analysis revealed strong positive correlations between different types of dementia, $CHADS_2$ score, and each individual factor of the $CHADS_2$ score (Table 6). Even after adjustment of variables and comorbidities including sex, coronary artery disease, chronic kidney disease, and use of aspirin, licodin, clopidogrel, ACEI, ARB, CCB, thiazide, or statins, the $CHADS_2$ score remained independently associated with the development of all-cause dementia [hazard ratio (HR) = 1.43; 95% confidence interval (CI), 1.37–1.49; $p < 0.001$], vascular dementia (HR = 1.54; 95% CI, 1.41–1.69; $p < 0.001$), and AD (HR = 1.40; 95% CI, 1.34–1.46; $p < 0.001$). Subsequent analysis of the hazard ratio of the $CHADS_2$ score in patients with different comobidities still showed similar results (Figs. S1–S3). (HTN = hypertension, DM = diabetes mellitus, CKD = chronic kidney disease, CHF = congestive heart failure, COPD = chronic obstructive pulmonary disease, VHD = vavular heart disease, CAD =coronary artery disease).

Table 4
Incidence (per 100 person-years) of dementia in patients with different $CHADS_2$ score.

$CHADS_2$ score	No. of patients	Cases of dementia	Person-years	Incidence (per 100 person-years)
0	1287	14	6342	0.22
1	2731	109	12,583	0.87
2	3192	181	12,981	1.39
3	3080	275	10,679	2.58
4	2578	257	8177	3.14
5	1846	224	5011	4.47
6	716	75	1544	4.86
Total	15,430	1135	57,316	1.98

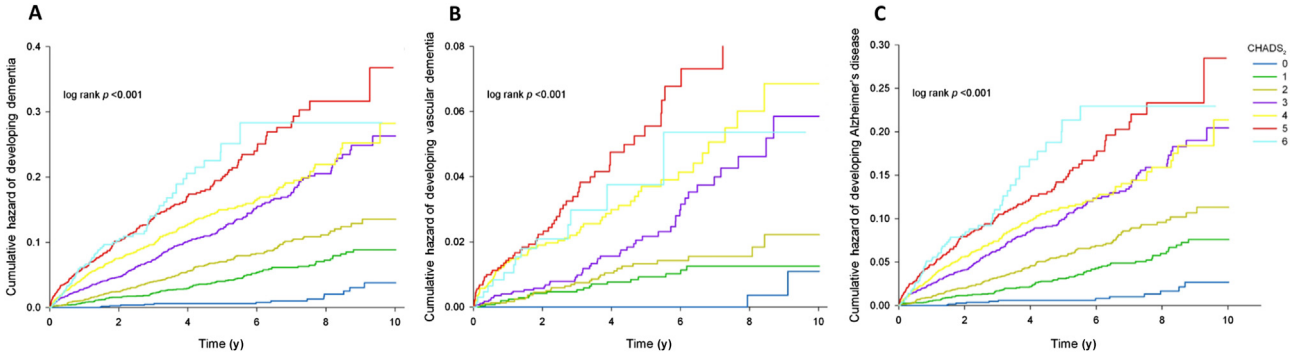

Fig. 3. Kaplan–Meier estimates of time to developing (A) all-cause dementia, (B) vascular dementia, and (C) Alzheimer's disease by $CHADS_2$ scores.

Table 5
The C-statistic of $CHARS_2$ score in prediction of the incidence of dementia, vascular dementia, and Alzheimer's disease.

	AUC	Criterion value	Sensitivity (%)	Specificity (%)
Dementia	0.633	>2	73.22	48.31
Vascular dementia	0.656	>2	77.59	47.11
Alzheimer's disease	0.622	>2	72.04	47.88

AUC = area under ROC curve.

4. Discussion

It has been reported that AF may increase the risk of developing dementia.[8] Our current study demonstrated that the $CHADS_2$ score is a useful parameter for predicting future risk of development of vascular dementia as well as AD, providing useful information to categorize AF patients at risk of developing dementia in the future.

More and more evidence suggests that AF may be a risk factor, or may even contribute directly to the development of dementia.[1,14] In addition to being associated with an approximately five-fold increase in the risk of clinical stroke,[15] AF has also been associated with more severe ischemic strokes and longer TIAs than emboli from carotid disease.[16,17] It is not difficult to connect AF with post-stroke dementia and all other types of vascular dementia. Much to our interest, AF is not only significantly related to vascular dementia, but also to AD.[18] A single cross-sectional study in 1997,[3] which included 6584 participants, showed an association between AF and dementia [odds ratio (OR) = 2.3; 95% CI, 1.4–3.7]. The strongest association was found not for vascular dementia, but rather for AD with cerebrovascular disease (OR = 4.1; 95% CI, 1.7–9.7). An association was also present between AF and pure AD (OR = 1.8; 95% CI, 1.7–9.7). Similar results have also been found in recent longitudinal studies and meta-analyses.[19,20] In a meta-analysis that included 21 observational studies,[20] AF was significantly associated with a higher risk for cognitive impairment in patients with a history of stroke [relative risk (RR) = 2.70; 95% CI, 1.82–4.00] than in those without (RR = 1.34; 95% CI, 1.13–1.58). Additionally, an observational study also found that warfarin use may reduce the incidence of dementia in AF patients.[21] Bunch et al[22] reported that patients who underwent AF ablation had a lower risk of AD than those who did not, suggesting a close relationship between dementia and AF, and that treatment for AF may potentially reduce the risk of dementia.

Several mechanisms have been proposed to explain the relationship between AF and vascular dementia. First, AF leads to incomplete draining of the left atrium and thus increased intracardiac thrombus formation, in turn increasing the risk of stroke and systemic embolism. In addition to stroke, patients with AF also suffer subclinical silent cerebral emboli.[23] Evidence of silent brain infarction on brain magnetic resonance imaging more than doubles the risk of dementia as noted in one neuropsychological study.[24] Second, AF increases the beat-to-beat variation of heart rate and cardiac output, resulting in cerebral hypoperfusion.[25] Other possible mechanisms include the hypercoagulability[21] and proinflammatory state presenting with AF.[26,27] Vascular and

Table 6
Cox proportional hazard analysis for the predictors of all-cause dementia, vascular dementia, and Alzheimer's disease.

Variable	All-cause dementia		Vascular dementia		Alzheimer's disease	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Age >75 y	3.75 (3.32–4.24)	<0.001	3.65 (2.80–4.76)	<0.001	3.78 (3.29–4.34)	<0.001
HTN	2.29 (1.94–2.72)	<0.001	2.08 (1.46–2.97)	<0.001	2.36 (1.94–2.86)	<0.001
DM	1.44 (1.28–1.63)	<0.001	1.51 (1.17–1.95)	0.002	1.43 (1.25–1.63)	<0.001
CHF	1.22 (1.08–1.37)	0.001	1.11 (0.86–1.43)	0.428	1.25 (1.09–1.42)	0.001
Stroke	2.39 (2.13–2.69)	<0.001	3.61 (2.77–4.69)	<0.001	2.15 (1.88–2.45)	<0.001
$CHADS_2$	1.48 (1.43–1.54)	<0.001	1.59 (1.46–1.72)	<0.001	1.45 (1.39–1.52)	<0.001
score	1.43 (1.37–1.49)[a]	<0.001[a]	1.54 (1.41–1.69)[a]	<0.001[a]	1.40 (1.34–1.46)[a]	<0.001[a]

ACEI = angiotensin-converting enzyme inhibitors; ARB = angiotensin II receptor blockers; CAD = coronary artery disease; CCB = calcium channel blocker; CHF = congestive heart failure; CI = confidence interval; CKD = chronic kidney disease; DM = diabetes mellitus; HR = hazard ratio; HTN = hypertension.
[a] Adjusted for sex, CAD, CKD, and medicines (include aspirin, licodin, clopidogrel, ACEI, ARB, CCB, thiazide, statins).

neurodegenerative pathologies were usually found together in patients with AD,[28,29] and were recently proposed to drive the progression of AD through different pathways.[30] In a population-based autopsy cohort study,[31] people with AF were 40–50% more likely to have gross infarcts and other neuropathologic changes, such as amyloid angiopathy, neuritic plaques, and neurofibrillary tangles. Although traditional theory regards vascular factors as purely associated with vascular dementia, several recent studies have suggested an increased risk of developing AD when exposed to the same vascular risk factors that caused stroke and vascular dementia.[32] Concomitant with aging, cerebrovascular disease and systemic vascular disorders may lead to reduction of regional blood flow and cause cerebral hypoperfusion.[33,34] There is a hypothesis based on experimental studies suggesting that small vessel disease in the brain causes chronic hypoperfusion, which may lead to pH changes, oxidative damage, amyloid β precursor protein expression, and subsequent aggregation of amyloid β peptides.[35] Moreover, the pathology of individuals with Alzheimer's disease had various features consistent with a blood–brain barrier breakdown, included thinning of the endothelium, loss of mitochondria, and thickening of basement membranes; this was thought to lead to toxic metabolites crossing into the brain and increasing focal amyloid β peptide accumulation in recent studies.[36] A small burden of cerebral ischemia caused by vascular factors may reveal the expression of amyloid β peptides and tangles associated with Alzheimer's disease. The association between vascular factors and Alzheimer's disease does not question nor negate the traditional degenerative mechanisms of Alzheimer's disease. In fact, vascular brain injury could act additively or synergistically with concomitant Alzheimer's disease pathology to produce more severe cognitive dysfunction.[32]

Currently known risk factors for dementia include age, genetic susceptibility, previous stroke, hypercholesterolemia, diabetes mellitus, hypertension, smoking, and metabolic syndrome.[37] Although AF and dementia share many underlying risk factors, there has been no good indicator for dementia occurrence in AF patients. The $CHADS_2$ score has recently been developed as a parameter for risk prediction for AF patients, whereby it is currently widely used for future stroke prediction and as a guide for anticoagulation prescription. In addition, it has been reported that the CHADS2 score could be used to predict AF recurrence after ablation, new AF occurrence after myocardial infarction,[38] and left atrium dysfunction in CAD patients,[6] offering multiple clinical applications for risk stratification.

Our study showed that high $CHADS_2$ score is a predictor of poor outcome among AF patients, not only for ischemic stroke, but also for the occurrence of dementia, providing practical guidance in clinical use. Although this study was not the first one to declare the association between $CHADS_2$ score and dementia,[39] our finding suggested that the predictive value of $CHADS_2$ score was good for both vascular dementia and AD. This finding implied that AF itself is an independent risk factor for dementia, regardless of whether or not there was clinical stroke event. $CHADS_2$ score is a simple and extensively applied tool for the evaluation of neurocardiovascular outcomes in AF patients.

As a population-based epidemiological study, the strength of our study is the large sample size enrolled from a population-based dataset, enabling us to trace prospectively the differences between the two groups. However, this study also has several limitations. First, the diagnosis of AF and dementia was identified using ICD-9 codes from a nationwide database set composed of hospitalization and outpatient clinic records. Similar methods for identifying AF using the same database have been used in other studies.[7,21,26,40] Although we did not verify each case ourselves because of the limitations of the database design, the diagnosis should be correct because each event had been identified for insurance claims purposes by qualified cardiologists or neurologist. Second, we did not subdivide study patients according to variable forms of AF, such as paroxysmal, persistent, and permanent AF. Some evidence has been reported suggesting there is no difference between those with paroxysmal AF and permanent AF in complications of AF, such as stroke.[41] Furthermore, there are no separate ICD-9 codes to be used for subdivision, and the future stroke risk of paroxysmal AF and permanent AF is similar.[7] Therefore, different types of AF were not identified separately in our study. Third, the diagnosis of AD and vascular dementia were also made by ICD codes. To define dementia and its subtypes by ICD codes, and not by traditional diagnostic criteria, would cause relatively inaccuracy of the diagnosis. Regarding dementia other than AD and vascular dementia, we did not enroll this population into our study because of the small case numbers and heterogeneity of their diagnosis. Additionally, because the dementia was identified using ICD-9 coding from neurologists' diagnosis, it is impossible to distinguish all mixed types of dementia and we did not have primary data for further study. Finally, certain confounders such as body mass index, blood pressure values, and lipid profiles were unavailable because of the limitations of the National Health Insurance database.

In conclusion, AF is associated with an increased risk of vascular dementia and AD. Increasing $CHADS_2$ score could be used as a predictor for the occurrence of dementia in patients with AF.

Acknowledgments

This study is based in part on data from the National Health Insurance Research Database provided by the Bureau of National Health Insurance, Department of Health and managed by the National Health Research Institutes in Taiwan. The present study was supported in part by research grants V99B1-011, V99C1-125, V100B-004, and V100B-013 from the Taipei Veterans General Hospital, Taipei, Taiwan; CI-97-13 and CI-98-16 from the Yen Tjing Ling Medical Foundation, Taipei, Taiwan; and NSC 100-2314-B-075-055 and UST-UCSD International Center of Excellence in Advanced Bio-Engineering NSC-99-2911-I-009-101-A2 from the National Science Council, Taiwan.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcma.2016.02.007.

References

1. Dublin S, Anderson ML, Haneuse SJ, Heckbert SR, Crane PK, Breitner JC, et al. Atrial fibrillation and risk of dementia: a prospective cohort study. *J Am Geriatr Soc* 2011;**59**:1369−75.
2. Bunch TJ, Weiss JP, Crandall BG, May HT, Bair TL, Osborn JS, et al. Atrial fibrillation is independently associated with senile, vascular, and Alzheimer's dementia. *Heart Rhythm* 2010;**7**:433−7.
3. Ott A, Breteler MMB, de Bruyne MC, van Harskamp F, Grobbee DE, Hofman A. Atrial fibrillation and dementia in a population-based study. The Rotterdam Study. *Stroke* 1997;**28**:316−21.
4. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *J Am Med Assoc* 2001;**285**:2864−70.
5. Chao TF, Lin YJ, Tsao HM, Tsai CF, Lin WS, Chang SL, et al. CHADS2 and CHA2DS2-VASc scores in the prediction of clinical outcomes in patients with atrial fibrillation after catheter ablation. *J Am Coll Cardiol* 2011;**58**:2380−5.
6. Azarbal F, Welles CC, Wong JM, Whooley MA, Schiller NB, Turakhia MP. Association of CHADS2, CHA2DS2-VASc, and R2CHADS2 scores with left atrial dysfunction in patients with coronary heart disease (from the Heart and Soul Study). *Am J Cardiol* 2014;**113**:1166−72.
7. Cheng YF, Leu HB, Su CC, Huang CC, Chiang CH, Huang PH, et al. Association between panic disorder and risk of atrial fibrillation: a nationwide study. *Psychosom Med* 2013;**75**:30−5.
8. Huang CC, Chung CM, Leu HB, Lin LY, Chiu CC, Hsu CY, et al. Diabetes mellitus and the risk of Alzheimer's disease: a nationwide population-based study. *PLoS One* 2014;**9**:e87095.
9. Chan WL, Yang KP, Chao TF, Huang CC, Huang PH, Chen YC, et al. The association of asthma and atrial fibrillation—a nationwide population-based nested case-control study. *Int J Cardiol* 2014;**176**:464−9.
10. Hsu CY, Huang CC, Chan WL, Huang PH, Chiang CH, Chen TJ, et al. Angiotensin-receptor blockers and risk of Alzheimer's disease in hypertension population—a nationwide cohort study. *Circ J* 2013;**77**:405−10.
11. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975;**12**:189−98.
12. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS−ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology* 1984;**34**:939−44.
13. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. 4th ed. Washington, DC: American Psychiatric Association; 2000.
14. Jacobs V, Cutler MJ, Day JD, Bunch TJ. Atrial fibrillation and dementia. *Trends Cardiovasc Med* 2015;**25**:44−51.
15. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K, et al. American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2009;**119**:480−6.
16. Anderson DC, Kappelle LJ, Eliasziw M, Babikian VL, Pearce LA, Barnett HJ. Occurrence of hemispheric and retinal ischemia in atrial fibrillation compared with carotid stenosis. *Stroke* 2002;**33**:1963−7.
17. Harrison MJ, Marshall J. Atrial fibrillation, TIAs and completed strokes. *Stroke* 1984;**15**:441−2.
18. Forti P. Atrial fibrillation is associated with an increased risk of cognitive impairment and dementia with or without a history of clinical stroke. *Evid Based Med* 2014;**19**:e3.
19. Udompanich S, Lip GY, Apostolakis S, Lane DA. Atrial fibrillation as a risk factor for cognitive impairment: a semi-systematic review. *Q J Med* 2013;**106**:795−802.
20. Kalantarian S, Stern TA, Mansour M, Ruskin JN. Cognitive impairment associated with atrial fibrillation: a metaanalysis. *Ann Intern Med* 2013;**158**:338−46.
21. Barber M, Tait RC, Scott J, Rumley A, Lowe GD, Stott DJ. Dementia in subjects with atrial fibrillation: hemostatic function and the role of anticoagulation. *J Thromb Haemost* 2004;**2**:1873−8.
22. Bunch TJ, Crandall BG, Weiss JP, May HT, Bair TL, Osborn JS. 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.
23. Ezekowitz MD, James KE, Nazarian SM, Davenport J, Broderick JP, Gupta SR, et al. Silent cerebral infarction in patients with nonrheumatic atrial fibrillation. The Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *Circulation* 1995;**92**:2178−82.
24. O'Connell JE, Gray CS, French JM, Robertson IH. Atrial fibrillation and cognitive function: case-control study. *J Neurol Neurosurg Psychiatry* 1998;**65**:386−9.
25. Lavy S, Stern S, Melamed E, Cooper G, Keren A, Levy P. Effect of chronic atrial fibrillation on regional cerebral blood flow. *Stroke* 1980;**11**:35−8.
26. Anderson JL, Allen Maycock CA, Lappé DL, Crandall BG, Horne BD, Bair TL, et al. Intermountain Heart Collaborative Study group. Frequency of elevation of C-reactive protein in atrial fibrillation. *Am J Cardiol* 2004;**94**:1255−9.
27. Crandall MA, Horne BD, Day JD, Anderson JL, Muhlestein JB, Crandall BG, et al. Atrial fibrillation and CHADS2 risk factors are associated with highly sensitive C-reactive protein incrementally and independently. *Pacing Clin Electrophysiol* 2009;**32**:648−52.
28. Kalaria RN. Cerebral vessels in ageing and Alzheimer's disease. *Pharmacol Ther* 1996;**72**:193−214.
29. Nishio K, Ihara M, Yamasaki N, Kalaria RN, Maki T, Fujita Y, et al. A mouse model characterizing features of vascular dementia with hippocampal atrophy. *Stroke* 2010;**41**:1278−84.
30. Kalaria RN, Ihara M. Dementia: vascular and neurodegenerative pathways—will they meet? *Nat Rev Neurol* 2013;**9**:487−8.
31. Dublin S, Anderson ML, Heckbert SR, Hubbard RA, Sonnen JA, Crane PK, et al. Neuropathologic changes associated with atrial fibrillation in a population-based autopsy cohort. *J Gerontol A Biol Sci Med Sci* 2014;**69**:609−15.
32. Viswanathan A, Rocca WA, Tzourio C. Vascular risk factors and dementia: how to move forward? *Neurology* 2009;**72**:368−74.
33. de la Torre JC. Hemodynamic consequences of deformed microvessels in the brain in Alzheimer's disease. *Ann N Y Acad Sci* 1997;**826**:75−91.
34. Bink DI, Ritz K, Aronica E, van der Weerd L, Daemen MJ. Mouse models to study the effect of cardiovascular risk factors on brain structure and cognition. *J Cereb Blood Flow Metab* 2013;**33**:1666−84.
35. Kalaria RN. The role of cerebral ischemia in Alzheimer's disease. *Neurobiol Aging* 2000;**21**:321−30.
36. Kalaria RN, Akinyemi R, Ihara M. Does vascular pathology contribute to Alzheimer changes? *J Neurol Sci* 2012;**322**:141−7.
37. Katayama T, Hasebe N. Angiotensin-receptor blockers, hypertension and Alzheimer disease—the entangled relationship. *Circ J* 2013;**77**:315−6.
38. Lau KK, Chan PH, Yiu KH, Chan YH, Liu S, Chan KH, et al. Roles of the CHADS2 and CHA2DS2-VASc scores in postmyocardial infarction patients: risk of new occurrence of atrial fibrillation and ischemic stroke. *Cardiol J* 2014;**21**:474−83.
39. Liao JN, Chao TF, Liu CJ, Wang KL, Chen SJ, Tuan TC, et al. Risk and prediction of dementia in patients with atrial fibrillation—a nationwide population-based cohort study. *Int J Cardiol* 2015;**199**:25−30.
40. Chiang CH, Huang CC, Chan WL, Huang PH, Chen YC, Chen TJ, et al. Herpes simplex virus infection and risk of atrial fibrillation: a nationwide study. *Int J Cardiol* 2013;**164**:201−4.
41. Hart RG, Pearce LA, Rothbart RM, McAnulty JH, Asinger RW, Halperin JL. Stroke with intermittent atrial fibrillation: incidence and predictors during aspirin therapy. Stroke Prevention in Atrial Fibrillation Investigators. *J Am Coll Cardiol* 2000;**35**:183−7.