Monotherapy of aspirin or warfarin for prevention of ischemic stroke in low-risk atrial fibrillation: A Easter Asian population-based study

Authors: Chieh-Yu Liu, Hui-Chun Chen

DOI: 10.5603/Cj.a2018.0051

Article type: Original articles

Submitted: 2017-07-06

Accepted: 2018-03-31

Published online: 2018-04-25

This article has been peer reviewed and published immediately upon acceptance. It is an open access article, which means that it can be downloaded, printed, and distributed freely, provided the work is properly cited. Articles in "Cardiology Journal" are listed in PubMed.
Monotherapy of aspirin or warfarin for prevention of ischemic stroke in low-risk atrial fibrillation: A Easter Asian population-based study

Running Title: Aspirin and warfarin for prevention of stroke in AF

Chieh-Yu Liu¹,², Hui-Chun Chen³

¹Biostatistical Consulting Lab, Department of Speech Language Pathology and Audiology, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan, R.O.C.
²Department of Midwifery and Women Health Care, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan, R.O.C.
³Department of Nursing, School of Nursing, National Taipei University of Nursing and Health Sciences, Taipei, Taiwan, R.O.C.

Address for correspondence: Associate Professor, Chieh-Yu Liu, PhD, 365, Biostatistical Consulting Lab, Department of Speech Language Pathology and Audiology, National Taipei University of Nursing and Health Sciences, Min-der Rd., Beitou district, Taipei City, Taiwan, R.O.C., tel: +886-2-28227101 ext. 3312/6203, fax: +886-2-23891404, e-mail: chiehyu@ntunhs.edu.tw

Abstract

Background: This study aimed to investigate the effectiveness of monotherapy aspirin and warfarin for stroke prevention in low-risk atrial fibrillation (AF) by using a population-based cohort study in Taiwan.

Methods: A newly diagnosed low-risk AF patient cohort were identified by using National Health Insurance Research Database (NHIRD) in Taiwan in 2008. The study
cohort was observed with a follow-up of 2 years to examine the onset of ischemic stroke (IS) (to 2010). The longitudinal data were analyzed by using generalized estimation equations (GEE).

**Results:** A total of 8,065 newly-diagnosed low-risk AF patients were identified in 2008. 7.4% were prescribed with aspirin and 4.6% were prescribed with warfarin. The GEE results showed that low-risk AF patients with hypertension who received warfarin were associated with a statistically significant 58.4% reduction of IS risk (OR = 0.416, p = 0.024, 95% CI 0.194–0.891). Additionally, low-risk AF patients with hyperlipidemia who received warfarin were associated with a 69.3% reduction of IS risk (OR = 0.307, p = 0.044, 95% CI 0.097–0.969).

**Conclusions:** Warfarin is suggested to be prescribed in preventing ischemic stroke for low-stroke-risk atrial fibrillation patients with hypertension and hyperlipidemia.

**Key words:** atrial fibrillation, aspirin, warfarin, ischemic stroke, hypertension, diabetes mellitus, hyperlipidemia

**Introduction**

The prevalence of atrial fibrillation (AF) is increasing in United States, European and Asian countries [1–3]. The incidence of AF was about 1.5 per 1000 person-years in Taiwan [4]. In recent years, although many novel oral anti-coagulants (NOACs) were proposed and have been demonstrated significantly effective in stroke prevention, especially in high stroke-risk AF patients, for example, rivaroxaban [5], dabigatran [6] and apixaban [7], but the NOACs were relatively more expensive compared to the two widely-used drugs: warfarin or aspirin. Consequently, warfarin or aspirin were considered to be prescribed for low-stroke-risk AF patients [8]. Although most published studies aimed mainly to investigate the effectiveness of
aspirin or warfarin in preventing stroke events for moderate and high-stroke-risk AF patients [9], there remain relatively few studies investigating the effectiveness of preventing stroke events for low-stroke-risk AF patients. One large scale study conducted in the United States found that, among AF patients with high-stroke-risk (CHADS2 score ≥ 2), 38.2% were treated with aspirin alone, 61.8% were treated with warfarin or non-vitamin K antagonist oral anticoagulation (OACs) [9], which indicated that prescribing aspirin or warfarin is still very common for high-stroke-risk AF patients. However, prescribing warfarin or aspirin to low-stroke-risk AF patients for prevention of stroke is still debatable among clinicians and cardiovascular physicians [10–12], especially for those with metabolic syndromes (including hypertension, diabetes mellitus [DM] and hyperlipidemia) [13]. However, prescribing aspirin or warfarin, or combining uses of both drugs to AF patients may be of concern for increasing the risk of unexpected bleeding [14–16], although the incidences of ischemic stroke (IS) is obviously lower for low-risk AF patients. Therefore, investigating the effectiveness of preventing IS of monotherapy of aspirin or warfarin in low-stroke-risk AF patients by using a large population-based database is needed [17]. Based on the above mentioned reasons, this study aimed to investigate the effectiveness in preventing IS of monotherapy of aspirin or warfarin in low-risk AF patients by using a population-based database, the National Health Insurance Research Database (NHIRD), in Taiwan.

**Methods**

**Study database**

This study used claims data from Taiwan’s National Health Insurance (NHI) program, which was launched by the Taiwan government in March, 1995 and provided comprehensive health care for 99.5% of its residents in 2010 [18]. The
NHIRD contains nationwide information including outpatient, inpatient, dentistry services, prescription drugs, and traditional Chinese medicine services. The diagnostic and procedure codes are based on the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) and Procedure Coding System (ICD-9-PCS).

**Ethics statement**

The Institutional Review Board of School of Nursing, National Taipei University of Nursing and Health Sciences approved this study (CN-IRB-2011-064). The National Health Research Institutes encrypt the personal information to protect individual information of patients. The National Health Insurance Administration guarantees the confidentiality of the personal and health information of patients.

**Study population**

An incidence-based patient cohort of newly diagnosed AF patients (ICD-9-CM code 427.31) who had at least two outpatient visits with primary disease of AF and whose CHA2DS2-VASc scores were < 2 (= 0 or 1) without a history of stroke events (including IS, hemorrhagic stroke [HS], and transient ischemic attack [TIA]) were identified and retrieved from NHIRD in 2008. This study cohort was followed up for up to 2 years (2010) to observe if they had an IS onset which was also defined by using ICD-9-CM code 430-438 [19]. In order to identify real low-risk AF patients, AF patients with severe baseline diseases were also excluded: cancers, coronary artery disease (CAD, including congenital heart defect [CHD], myocardial infarction [MI], and heart failure [HF]), kidney failure (including chronic kidney failure [CKD]), abnormal renal and liver function as well as peripheral artery disease (PAD). Apart from that, based on one recently published study [11] which showed that combining
the use of aspirin and warfarin may result in unexpected vascular diseases and some cardiovascular disorders, therefore, patients who used concomitant drugs of both aspirin and warfarin were also excluded. The enrollment scheme of study patients is shown in Figure 1.

**Covariate assessment**

The covariate variables including sex, age, baseline hypertension status, DM status and hyperlipidemia status were also taken into account. Additionally, to identify the low-stroke-risk AF patients, CHA$_2$DS$_2$-VASc score was adopted and was defined as: congestive HF, hypertension, age ($\geq$ 65 = 1 point, $> 75 = 2$ points), diabetes, previous stroke or TIA (2 points), vascular disease (including PAD, previous MI, aortic atheroma), and sex (female gender). In this study, the study cohort were all with CHA$_2$DS$_2$-VASc score $< 2$ (0 or 1), which was considered suitable for defining “low-risk” for East Asian AF patients [20, 21]. Besides, the HAS-BLED [22] score was also calculated based on ICD-9-CM code. The HAS-BLED scoring system mainly calculates the risk of major bleeding, which was defined as intracranial bleeding, bleeding requiring hospitalization, a hemoglobin decrease of more than 2 g/dL, or the need for transfusion secondary to bleeding.

**Statistical analysis**

The longitudinal data were analyzed by using generalized estimation equations (GEE). GEE is a comprehensive extension of generalized linear models (GLZM) in that they allow for adjusting correlation structure between observations for each subject. The strength of GEE is that they do not require precise specification of multivariate distribution but only of the structure of means or logits for each repeated measurement [23]. In this study, the GEE for longitudinal binary outcome was used
(with/without IS) [24]. The modeling was as below:

Define the marginal mean and variances of \( y_{ij} \) as

\[
\mu_{ij} = E(y_{ij}|X_{ij}) \quad \text{and} \quad \text{Var}(y_{ij}) = \mu_{ij}(1 - \mu_{ij})
\]

Then the marginal logit link function was used:

\[
\text{logit}(\mu_{ij}) = \log\left(\frac{\mu_{ij}}{1 - \mu_{ij}}\right) = \beta'X_{ij}
\]

where \( \beta \) is the GEE coefficient vector to be estimated. The GEE estimator \( \hat{\beta} \) of \( \beta \) is obtained through estimating the following GEE model:

\[
\sum_{i=1}^{n} D'_i V_i^{-1} (y_i - \mu_i) = 0
\]

where \( \mu_i = (\mu_{i1}, ..., \mu_{ni})' \), \( D'_i = \frac{\partial \mu_i}{\partial \beta} \) and \( V_i \) is the working covariance matrix of \( y_i \), which can be expressed as

\[
V_i = A_i^\frac{1}{2} R_{wi}(\gamma) A_i^\frac{1}{2}, \quad \text{where} \quad R_{wi}(\gamma)
\]

is a working correlation matrix with parameter \( \gamma \), which can be estimated from empirical data. In this study, a compound symmetry (or called exchangeable) form of working correlation matrix was used as follows:

\[
R_w = \begin{bmatrix}
1 & \rho & \cdots & \rho \\
\rho & 1 & \rho & \rho \\
\vdots & \vdots & \ddots & \vdots \\
\rho & \cdots & \rho & 1 \\
\end{bmatrix}
\]

where \( \rho \) was estimated from the data. The odds ratio (OR) of IS of AF patients with and without taking aspirin and warfarin were calculated. The results were expressed using ORs with 95% confidence intervals (CIs). My Structured Query Language (MySQL) was used for extraction, linkage, and processing of data. All statistical analyses were performed using IBM SPSS statistical software Version 20 (IBM Corp., New York, NY, USA). A two-tailed \( p < 0.05 \) was considered statistically significant.

**Results**

This study recruited 8,065 low risk AF patients aged \( \geq 20 \) years old, who had at
least two outpatient visits with a primary diagnosis of AF, whose CHA₂DS₂-VASc score < 2 (= 0 or 1), without a history of baseline events of stroke (including HS, IS, and TIA) and without severe baseline diseases which include: cancers, CAD (including CHD, MI, and HF), kidney failure (including CKD) and PAD in 2008. The mean age was 55.95 years old (standard deviation [SD] = 11.60), 78.7% were male and 21.3% were female. Among the study cohort, 4.9% of patients had hypertension, 1.9% with DM, and 2.4% with hyperlipidemia. Additionally, 57.7% of patients were with CHA₂DS₂-VASc score = 0 and 42.3% were with CHA₂DS₂-VASc score = 1. Among the study cohort, 7.4% took aspirin and 4.6% took warfarin in 2008 (Table 1).

The distribution of HAS-BLED score was: 89.1% were with 0, 9.5% with 1, and 1.4% with 2. Regarding major bleeding events, according to the database used in this study, there were no major bleeding events found in this study database (Table 1). The incidences of subsequent IS of this study cohort were 2.1% in 2009 and 2.4% in 2010. The results of the GEE model showed that low-risk AF patients who were with hypertension and received warfarin were associated with a statistically significant 58.4% reduction of IS risk (OR = 0.416, p = 0.024, 95% CI 0.194–0.891).

Additionally, low-risk AF patients with hyperlipidemia and received warfarin were associated with a statistically significant 69.3% reduction in IS risk (OR = 0.307, p = 0.044, 95% CI 0.097–0.969) (Table 2).

**Discussion**

This study used the Taiwan NHIRD, which is a large-scale population-based database to investigate the effectiveness of preventing IS with a monotherapy of aspirin or warfarin among low-stroke-risk AF patients. The results of this study showed that warfarin can help in preventing IS for low-risk AF patients with hypertension and hyperlipidemia. This study agreed with related published studies
which defined low-risk solely used CHA2DS2-VASc score [25, 26]. Regarding rates of receiving aspirin or warfarin, one published study, also using Taiwan NHIRD between 2001 to 2008 showed that the rates of general AF patients (including low-, medium- and high-risk), who received warfarin, aspirin, or no treatment in Taiwan was 16%, 62%, and 22% [27]. In comparison with the results of the present study, for low-risk AF patients, 7.4% had a monotherapy of aspirin and 4.6% had a monotherapy of warfarin, which were lower than the previously mentioned study [27]. In addition, one published result of a large scale study conducted in the United States [9] in a high-risk group showed that 38.2% of AF patients receiving aspirin, and 61.8% receiving warfarin or non-vitamin K antagonist oral anti-coagulants (OACs).

Regarding the use of aspirin for low-risk AF patients, the results of this study did not show a statistically significant effectiveness, which agreed with published studies demonstrating that aspirin had limited or non-significant effectiveness for preventing IS in recent years [28, 29]. A randomized clinical trial conducted in Japan showed that low-dose aspirin cannot provide significant effectiveness for stroke prevention among low-risk AF patients [29]. In 2016, the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology issued Guidelines for the management of AF in Taiwan, which stated that aspirin did not benefit in stroke prevention in patients with nonvalvular AF, dual antiplatelet therapy (DAPT) of aspirin and clopidogrel did not benefit in the prevention of stroke in patients with nonvalvular AF, unless under other therapeutic indications, such as in patients with acute coronary syndrome (ACS) and receiving stenting therapy [30]. The results of the present study may support the management guideline. Additionally, one expert opinion proposed that aspirin may be over-prescribed among AF patients [31], probably due to the low price of aspirin compared with warfarin [32]. Therefore, although aspirin was widely prescribed, the results of this study showed that aspirin did not benefit in preventing IS for low-risk
AF patients.

In addition, it is worth noting that low-risk newly diagnosed AF patients still may have a risk of IS onset in the following 2 years (2.1~2.4% as shown in the present study), which was similar with one large scale study conducted in European countries which showed that IS incidence rates were 2.1, 3.0, and 4.2% for paroxysmal, persistent, and permanent AF, respectively [33]. In summary, results of this study can provide some clinical implications: first, intensive monitoring of stroke events (including HS, IS and TIA), which is strongly suggested and some associated symptoms, for example, FAST [34]: face drooping, arm weakness, speech difficulty and time to call emergency help (ex. 911) and low-risk AF patients should be carefully reminded of this.. Second, warfarin can help in preventing ischemic stroke for low-risk AF patients with hypertension and hyperlipidemia.

This study had some limitations. First, the NHIRD did not provide information of potential confounders including smoking, alcohol drinking, life style, diet and other factors, which are associated with the risk of IS. Second, AF patients can buy over-the-counter (OTC) aspirin in drug stores, which were not recorded in NHIRD, so that some AF patients may use warfarin concurrently with aspirin, which will result in an underestimate for the number of patients using aspirin. One published study proposed that combining the use of aspirin and warfarin was inappropriate [11], it is believed that a number of AF patients may concurrently use both aspirin and warfarin, which could not be identified in NHIRD. Third, due to the nature of the study database, it was an outpatient claims database which provided only drug prescriptions without dosage information, therefore the dose effect could not be analyzed and was regarded as another study limitation.. Fourth, published studies have shown that poor adherence to anticoagulation guidelines in patients with AF [35–37]. Although we may code one AF patient with the prescription of aspirin or warfarin from the claims
database, it could not be verified that the information of drug compliance of the recruited AF patients in this study was carried out. Lastly, although there were no major bleeding events found in this study database, there were probably minor bleeding events which were not recorded in NHIRD, which was also regarded as a study limitation.

Conclusions

The present study used a large scale population-based database which showed that monotherapy of warfarin was suggested in prescribing for the prevention of IS in low-stroke-risk AF patients, especially for low-risk AF patients with hypertension and hyperlipidemia.

Acknowledgments

We thank the National Health Research Institutes (NHRI) for maintaining the National Health Insurance Research Database (NHIRD), and we thank the National Health Insurance Administration for managing the NHIRD.

Conflict of interest: None declared

References


Figure 1. Enrollment scheme of this study; ICD-9-PCS — Procedure Coding System.

Newly Diagnosed with Atrial Fibrillation who had at least two outpatient visits with ICD-9-CM code = 427.31 in 2008
N=32,362

Excluded:
1. Confirmed stroke diagnoses histories: including Ischemic stroke (IS), hemorrhagic and transient ischemic attack (TIA)
2. Baseline severe diseases: including cancers, coronary artery disease (CAD, including congenital heart defect (CHD), myocardial infarction, heart failure), kidney failure (including chronic kidney failure (CKD)), abnormal renal and liver function and peripheral artery disease (PAD).
3. CHA2DS2-VASc score $\geq 2$
4. Concomitant drug use of aspirin and warfarin

Newly Diagnosed Atrial Fibrillation Patients with Low-Stroke-Risk in 2008
N=8,065

Followed up to 2 years to observe the onset of ischemic stroke (IS) till 2010, which was defined using ICD-9-CM code = 430-438
Table 1. Demographic information of study cohort in 2008 (n = 8,065)

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>55.95 ± 11.60</td>
<td></td>
</tr>
<tr>
<td>Sex:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1,719</td>
<td>21.3</td>
</tr>
<tr>
<td>Male</td>
<td>6,346</td>
<td>78.7</td>
</tr>
<tr>
<td>Hypertension:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With</td>
<td>396</td>
<td>4.9</td>
</tr>
<tr>
<td>Without</td>
<td>7,669</td>
<td>95.1</td>
</tr>
<tr>
<td>Diabetes mellitus:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With</td>
<td>155</td>
<td>1.9</td>
</tr>
<tr>
<td>Without</td>
<td>7,910</td>
<td>98.1</td>
</tr>
<tr>
<td>Hyperlipidemia:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With</td>
<td>193</td>
<td>2.4</td>
</tr>
<tr>
<td>Without</td>
<td>7,872</td>
<td>97.6</td>
</tr>
<tr>
<td>Aspirin:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking</td>
<td>599</td>
<td>7.4</td>
</tr>
<tr>
<td>Not taking</td>
<td>7,466</td>
<td>92.6</td>
</tr>
<tr>
<td>Warfarin:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taking</td>
<td>372</td>
<td>4.6</td>
</tr>
<tr>
<td>Not taking</td>
<td>7,693</td>
<td>95.4</td>
</tr>
<tr>
<td>CHA2DS2-VASc score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>4,653</td>
<td>57.7</td>
</tr>
<tr>
<td>1</td>
<td>3,412</td>
<td>42.3</td>
</tr>
<tr>
<td>HAS-BLED score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7,187</td>
<td>89.1</td>
</tr>
<tr>
<td>1</td>
<td>763</td>
<td>9.5</td>
</tr>
<tr>
<td>2</td>
<td>115</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Table 2. The results of generalized estimation equations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>OR</th>
<th>95% CI for OR</th>
<th></th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
</tr>
<tr>
<td><strong>Main effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Intercept)</td>
<td>0.003</td>
<td>0.002</td>
<td>0.005</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>Sex (male vs. female)</td>
<td>0.972</td>
<td>0.687</td>
<td>1.378</td>
<td>0.875</td>
</tr>
<tr>
<td>Age</td>
<td>1.010</td>
<td>0.998</td>
<td>1.023</td>
<td>0.106</td>
</tr>
<tr>
<td>Year</td>
<td>2.697</td>
<td>2.403</td>
<td>3.027</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>ASPIRIN</td>
<td>2.377</td>
<td>1.427</td>
<td>3.961</td>
<td>0.001**</td>
</tr>
<tr>
<td>WARFARIN</td>
<td>7.345</td>
<td>4.419</td>
<td>12.208</td>
<td>&lt; 0.001***</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.200</td>
<td>1.409</td>
<td>3.436</td>
<td>0.001**</td>
</tr>
<tr>
<td>DM</td>
<td>1.760</td>
<td>0.694</td>
<td>4.464</td>
<td>0.234</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>3.929</td>
<td>1.516</td>
<td>10.182</td>
<td>0.005**</td>
</tr>
<tr>
<td><strong>Interaction effects</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASPIRIN × Hypertension</td>
<td>1.540</td>
<td>0.737</td>
<td>3.218</td>
<td>0.251</td>
</tr>
<tr>
<td>ASPIRIN × DM</td>
<td>1.983</td>
<td>0.406</td>
<td>9.693</td>
<td>0.398</td>
</tr>
<tr>
<td>ASPIRIN × Hyperlipidemia</td>
<td>1.382</td>
<td>0.550</td>
<td>3.469</td>
<td>0.491</td>
</tr>
<tr>
<td>WARFARIN × Hypertension</td>
<td><strong>0.416</strong></td>
<td><strong>0.194</strong></td>
<td><strong>0.891</strong></td>
<td><strong>0.024</strong>*</td>
</tr>
<tr>
<td>WARFARIN × DM</td>
<td>0.711</td>
<td>0.119</td>
<td>4.238</td>
<td>0.708</td>
</tr>
<tr>
<td>WARFARIN × Hyperlipidemia</td>
<td><strong>0.307</strong></td>
<td><strong>0.097</strong></td>
<td><strong>0.969</strong></td>
<td><strong>0.044</strong>*</td>
</tr>
</tbody>
</table>

CI — confidence interval; DM — diabetes mellitus; OR — odds ratio; *p < 0.05; **p < 0.01; ***p < 0.001