Antithrombotic Treatment May Reduce Mortality Among New-Onset Atrial Fibrillation Patients with Gray-Zone Risk of Stroke
A Population-Based Cohort Study

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Summary

In clinical practice, some atrial fibrillation (AF) patients were classified as having low and moderate stroke risk by the CHADS2 score (≤1) in 2001 but in 2012 they were not truly classified as low risk of stroke according to the CHA2DS2-VASc score (≥2) (defined gray zone). Therefore, a treatment gap exists in gray zone AF patients. This study aimed to evaluate whether gray zone AF patients could benefit from reduced all-cause mortality under antithrombotic treatment. This was a longitudinal cohort study performed using data from claim forms submitted to the Taiwan Bureau of National Health Insurance from January 2000 to December 2011. The new-onset AF patients consisted of a gray zone cohort with a total of 1237 patients being enrolled. The primary outcome was all-cause mortality between 2001 and 2011. Patients in the gray zone receiving antithrombotic treatment had a significant reduction in all-cause mortality [hazard ratio (HR): 0.21; 95% confidence interval (CI): 0.16-0.28] compared with the no treatment group [warfarin only: HR, 0.28 (95% CI, 0.15-0.52); warfarin + Aspirin: HR, 0.21(95% CI, 0.15-0.30); and Aspirin only: HR, 0.22 (95% CI, 0.16-0.29)]. All-cause mortality was notably increased when any of the following risk factors were present: age 65-74 years, age ≥75 years, chronic kidney disease, and vascular disease. We concluded that AF patients in the gray zone must receive either anticoagulant and/or antiplatelet treatment and there is a lower mortality in these groups during long-term follow-up. Further investigation is needed to observe whether the antithrombotic drugs have benefits for patients with AF with a CHA2DS2-VASc score <2.

Key words: CHADS2 score, CHA2DS2-Vasc score

Atrial fibrillation (AF) is a common cardiovascular disease in the elderly population worldwide.1,2) This condition is associated with an increased risk of arterial thromboembolism and ischemic stroke.3) AF reportedly causes approximately ≥15% of all strokes and increases the risk of ischemic stroke by around 5-fold compared with the non-AF population.4,5) Important, effective prevention of stroke and thromboembolism requires anticoagulant or antiplatelet agents.5,6) However, anticoagulant and antiplatelet treatments are underused, which might be related to the uncertain risk of thromboembolism, particularly in elderly individuals.

Comprehensive risk stratification is crucial to guiding the treatment of patients with AF. The congestive heart failure, hypertension, aged > 75 years, diabetes mellitus, and prior stroke or transient ischemic attack (CHADS2) score for stroke risk stratification was determined according to the method of Gage, et al.7) A CHADS2 score of 0 indicates low risk, 1 point indicates moderate risk, and ≥2 points indicates high risk. The revised American College of Cardiology (ACC)/American Heart Association Task Force (AHA)/European Society of Cardiology (ESC) 2006 guideline recommends either aspirin or warfarin for the prevention of ischemic stroke in patients with AF with a CHADS2 score of 18) and warfarin use for those with a CHADS2 score ≥2.

The 2006 ACC/AHA/ESC guidelines for the management of patients with AF mention the following additional risk factors: female sex, age 65-74 years, coronary heart disease, and peripheral artery disease. The score calculated using these additional risk factors is called the CHA2DS2-VASc score.9) A 2012 update of the ESC guidelines for
the management of AF recommends use of the CHA2DS2-VASc score to assess the stroke risk of patients with non-valvular AF, particularly to identify patients at truly low stroke risk.\(^{40}\) The CHA2DS2-VASc score takes sex into account and is a more sensitive scoring system for differentiating truly low-risk patients from those who may appear to be at low risk according to their CHADS2 score but are actually at considerable risk.

Use of the CHADS2 and CHA2DS2-VASc scores for the prediction of all-cause mortality, especially among patients with AF, is rare. These scores have been applied in patients with heart failure\(^{11}\) and those with sick sinus syndrome.\(^{12}\) In the Fushimi AF registry\(^{13}\) advanced age, being underweight, a previous stroke/transient ischemic attack (TIA), heart failure, chronic kidney disease (CKD), and anemia were reported to be independently associated with death among Japanese patients with non-anticoagulated AF. Therefore, using the population-based Taiwan National Health Insurance data, we performed a retrospective cohort study to investigate mortality after warfarin or aspirin treatment in patients with AF who were at low or intermediate risk for stroke on the basis of their CHADS2 score (0 or 1) but at higher risk according to the CHA2DS2-VASc score (≥ 2).

**Methods**

**Patient selection:** We conducted a nationwide cohort study by retrieving data for all patients with AF in the Taiwan National Health Insurance Research Database (NHIRD), including all inpatient and outpatient medical claims data. The NHIRD has been described in detail in previous studies.\(^{14,15}\) Briefly, it consists of detailed health care data of more than 23 million enrollees, representing more than 99% of Taiwan’s entire population. The accuracy of diagnosis of major diseases in the NHIRD, such as stroke, has been validated.\(^{5,16}\) In this study, we used an anonymized claims database provided by Taiwan National Health Insurance, and the principal investigator was requested to sign an agreement regarding compliance with the Computer-Processed Personal Data Protection Act during the proposal application. This study was approved by the ethics committee of Fong Yuan Hospital (FY-15030). The ethics committee waived the need for patient consent for this study.

**Protocol for study:** We identified all patients with new-onset AF from January 1, 2001 to December 31, 2006. From among them, we selected only the reclassification of patients who were initially classified as having a lower risk of stroke according to a CHADS2 score ≤ 1 but were reassigned as having a high risk of stroke according to a CHA2DS2-VASc score ≥ 2. A CHADS2 score ≤ 1 but a CHA2DS2-VASc score ≥ 2 was defined as a gray zone. We used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), to define AF (ICD-9-CM code 427.31), congestive heart failure (ICD-9-CM code 428.0), hypertension (ICD-9-CM codes 402-405), diabetes mellitus (ICD-9-CM code 250), stroke/TIA (ICD-9-CM codes 430-438), vascular disease (ICD-9-CM codes 440.2-440.29), CKD (ICD-9-CM codes 585, 586), old myocardial infarction (ICD-9-CM code 412), and hyperlipidemia (ICD-9-CM codes 272.0-272.9). The inclusion criteria were as follows: (1) new-onset AF between 2001 and 2006, (2) age ≥ 50 years, (3) no stroke history before AF diagnosis, and (4) both CHADS2 score ≤ 1 and CHA2DS2-VASc score ≥ 2. We excluded the patients who had acute myocardial infarction before AF onset. Patients were divided into 3 age groups according to the classification of the CHA2DS2-VASc scoring system: (1) 50-64 years, (2) 65-74 years, and (3) ≥ 75 years. The study participants were followed until the occurrence of mortality between 2001 and 2011.

**Study cohorts:** Patients who were newly diagnosed with AF in the gray zone were divided into 2 cohorts based on their use of medicine or not. The patients were analyzed according to treatment as those receiving anticoagulants (warfarin) only, antiplatelets (aspirin) only, and anticoagulants plus antiplatelets. The treatment details were obtained through medication records beyond 6 months after AF diagnosis between 2001 and 2006. Moreover, whether the participants were receiving anticoagulant or/and antiplatelet therapy was determined at the 6th month after AF diagnosis by medication records.

**Covariate assessment:** The risk evaluation based on CHADS2 and CHA2DS2-VASc scores was performed during the contemporary period by using ICD-9-CM coding while new-onset AF was confirmed. The risk factors for comorbidities, CHADS2 scores, and CHA2DS2-VASc scores were evaluated for congestive heart failure, hypertension, diabetes mellitus, stroke/TIA, vascular disease, CKD, and hyperlipidemia. The CHA2DS2-VASc score and CHADS2 score were calculated on the basis of summation of the following risk factors: 2 points for age ≥75 years or previous stroke/TIA, and 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65-74 years, and female sex.\(^{17}\)

**Main outcome measurements:** The primary outcome was all-cause mortality. All-cause mortality was defined by the registration of the date of death by National Health Insurance.\(^{16}\) The diagnoses of the following mortality were selected by the definition, but the period was between 2001 and 2011, after the occurrence of AF was confirmed.

**Statistical analysis:** Continuous variables were summarized as the mean and standard deviation, whereas categorical variables were summarized as counts and percentages. Variables were compared between groups by using \(t\) tests for continuous variables and chi-square tests for categorical variables. This study was designed to reveal whether warfarin or aspirin treatment in patients with AF with a gray zone risk of stroke was associated with lower mortality. In univariate analysis, the Kaplan-Meier method and the log-rank test were applied to examine whether the hazard ratios (HRs) with 95% confidence intervals (CIs) of treatment groups differed from those of the nontreatment group. Additional adjusted multivariate Cox proportional hazards regression models that included sex, age, and comorbidities were implemented. Finally, time-to-event comparisons among the 4 subgroups were performed using Kaplan-Meier survival curve analysis. Time-dependent bias was adjusted for by excluding the mortality cases in the nontreatment group before the medical treatment was confirmed (with a lag time of approxi-
Table I.

| CHADS2/CHA2DS2-VASc Score | Treatment Group | Nontreatment Group |
|---------------------------|----------------|-------------------|
| 0                         | 925            | 312               |
| 1                         | 509            | 74                |
| 2                         | 503            | 30                 |
| 3                         | 509            | 74                |

Figure 1. The flowchart of study.

Results

Baseline characteristics: Among the 8451 patients with new-onset AF occurring between 2001 and 2006, 1237 patients were included in our analysis (Figure 1). The mean duration of follow-up was 6.8 years. The duration of follow-up was significantly different between the treatment and nontreatment group. Most of the patients were in the treatment group (n = 925, 74.8%), and the remainder were in the nontreatment group (n = 312, 25.2%). Of the patients in the treatment group, 55.0% (n = 509) received aspirin, 8.0% (n = 74) received warfarin, and 37.0% (n = 342) received aspirin plus warfarin. The age distribution ratio was significantly different between the treatment and nontreatment groups. The majority of the patients in the nontreatment group were aged ≥75 years (46.2%), whereas those in the treatment group were aged 65-74 years (66.3%). Elderly patients (≥75 years of age) were less likely to receive treatment (46.2% without treatment vs. 11.5% with treatment; P < 0.05). The sex distribution did not differ between the treatment and nontreatment groups (Table I).

No difference in the distribution of the CHADS2 scores was noted. By contrast, for the CHA2DS2-VASc scores, the treatment group mostly had scores of 2 (62.8%) and 3 (32.2%), whereas a sizable portion of the nontreatment group had scores of 4 (21.8%) and an equal number of scores of 2 (39.1%) and 3 (39.1%) (Table I).

Regarding comorbidities, significantly more hypertension (59.8% versus 30.1%; P < 0.001) and hyperlipidemia (17.1% versus 5.1%; P < 0.001) cases were observed in the treatment group. There were slightly more CKD cases in the nontreatment group (7.7% versus 3.9%; P = 0.056).

Clinical outcome: The main emphasis was on death. A significant reduction in the mortality rates was observed in the treatment group (n = 265, 28.6%) compared with in the nontreatment group (n = 236, 75.6%; P < 0.001). The multivariate Cox proportional hazards regression model revealed that, compared with the nontreatment group, the application of antithrombotic treatment resulted in reduced mortality (adjusted HR, 0.21; 95% CI, 0.16-0.28). The benefits were similar among the warfarin-only (adjusted HR, 0.28; 95% CI, 0.15-0.52), aspirin-only (adjusted HR, 0.22; 95% CI, 0.16-0.29), and warfarin-plus-aspirin (adjusted HR, 0.21; 95% CI, 0.15-0.30) groups. Elderly patients had a higher risk of mortality (aged ≥75 years adjusted HR, 3.1; 95% CI, 1.47-6.55; aged 65-74 years adjusted HR, 2.08; 95% CI, 1.28-3.36). The variable of sex did not influence mortality. The presence of hypertension, diabetes mellitus, or hyperlipidemia showed no impact on mortality. CKD and vascular disease caused significantly increased mortality, with adjusted HRs of 1.72 (95% CI, 1.08-2.75) and 1.81 (95% CI, 1.22-2.68), respectively (Table II). Finally, a significant reduction in the mortality rates was observed in the treatment group compared with in the nontreatment group after adjusting for multivariate variables including the CHADS2/CHA2DS2-VASc score (P < 0.001).

The Kaplan-Meier survival curves for mortality in the treatment and nontreatment groups revealed some differences in the beginning, with P < 0.001 by log-rank test. The warfarin-only, warfarin-plus-aspirin, and aspirin-only treatments had similar protective benefits (Figure 2A). After adjustment for the time lag between the treatment and nontreatment groups, the treatment group still demonstrated significant protective effects for all-cause mortality (Figure 2B). The adjustment was achieved by excluding the mortality cases in the nontreatment group that occurred before the antithrombotic treatment was confirmed (lag time of approximately 6 months).

Discussion

In this pilot study, we assessed the strength of the protective effects of anticoagulant and/or antiplatelet treatment on long-term mortality among Asian patients with a low risk of stroke according to a CHADS2 score but were reassigned as having a high risk of stroke according to a CHA2DS2-VASc score for nonvalvular AF. The results reveal that both antiplatelet and anticoagulant treatments provide crucial protection for survival, especially among patients with a gray zone risk of stroke.

In clinical practice, patients with AF who have a CHA2DS2-VASc score of 0 have a truly low risk of stroke/thromboembolism that is not significantly different among
Table 1. Baseline Characteristics of All Patients

| Variable | Total (n = 1237) | Without treatment* (n = 312) | With treatment (n = 925) | P value |
|----------|------------------|-----------------------------|--------------------------|---------|
| Duration of follow-up, years, mean ± SD | 6.8 ± 2.9 | 5.2 ± 3.4 | 7.4 ± 2.6 | <0.0001 |
| Age at entry, years, mean ± SD | 70.4 ± 8.4 | 75.0 ± 10.1 | 68.8 ± 7.2 | <0.0001 |
| 50-64, n (%) | 244 (19.7) | 38 (12.2) | 206 (22.3) | <0.0001 |
| 65-74, n (%) | 743 (60.1) | 130 (41.7) | 613 (66.3) | |
| ≥ 75, n (%) | 250 (20.2) | 144 (46.2) | 106 (11.5) | |
| Gender | | | | |
| Female, n (%) | 610 (49.3) | 150 (48.1) | 460 (49.7) | 0.730 |
| Male, n (%) | 627 (50.7) | 162 (51.9) | 465 (50.3) | |
| Comorbidity | | | | |
| Hypertension, n (%) | 647 (52.3) | 94 (30.1) | 553 (59.8) | <0.0001 |
| Diabetes mellitus | 50 (4.0) | 8 (2.6) | 42 (4.5) | 0.279 |
| Hyperlipidemia, n (%) | 174 (14.1) | 16 (5.1) | 158 (17.1) | 0.000 |
| Congestive heart failure (CHF), n (%) | 205 (16.6) | 46 (14.7) | 159 (17.2) | 0.462 |
| Chronic kidney disease (CKD), n (%) | 60 (4.9) | 24 (7.7) | 36 (3.9) | 0.056 |
| Vascular disease, n (%) | 122 (9.9) | 26 (8.3) | 96 (10.4) | 0.461 |
| CHADS2 Score, mean ± SD | 0.9 ± 0.3 | 0.9 ± 0.2 | 0.9 ± 0.3 | 0.830 |
| ≥ 0, n (%) | 84 (6.8) | 20 (6.4) | 64 (6.9) | |
| 1, n (%) | 1153 (93.2) | 292 (93.6) | 861 (93.1) | |
| 2, n (%) | 703 (56.8) | 122 (39.1) | 581 (62.8) | |
| 3, n (%) | 420 (34.0) | 122 (39.1) | 298 (32.2) | |
| 4, n (%) | 114 (9.2) | 68 (21.8) | 46 (5.0) | |
| CHADS2-VASc Score, mean ± SD | 2.5 ± 0.7 | 2.8 ± 0.8 | 2.4 ± 0.6 | <0.0001 |
| CHADS2-VASc Score > 0, n (%) | | | | |
| Treatment and Nontreatment Groups | | | | |
| Without treatment | 1.00 | - | - | |
| With treatment | 0.21* | 0.16 | 0.28 | |
| Treatment with Warfarin only | 0.28* | 0.15 | 0.52 | |
| Treatment with Aspirin + Warfarin both | 0.21* | 0.15 | 0.30 | |
| Treatment with Aspirin only | 0.22* | 0.16 | 0.29 | |
| Age at entry, years | | | | |
| 50-64 | 1.00 | - | - | |
| 65-74 | 2.08* | 1.28 | 3.36 | |
| ≥ 75 | 3.10* | 1.47 | 6.55 | |
| Gender | | | | |
| Female | 1.00 | - | - | |
| Male | 1.26 | 0.95 | 1.68 | |
| Comorbidity | | | | |
| Hypertension | 0.61 | 0.36 | 1.04 | |
| Diabetes mellitus | 0.64 | 0.26 | 1.55 | |
| Hyperlipidemia | 0.64 | 0.38 | 1.06 | |
| Congestive heart failure (CHF) | 1.18 | 0.66 | 2.11 | |
| Chronic kidney disease (CKD) | 1.72* | 1.08 | 2.75 | |
| Vascular disease | 1.81* | 1.22 | 2.68 | |

*Adjusted for age, gender, heart failure, hypertension, diabetes mellitus, vascular disease, chronic kidney disease, and hyperlipidemia. **Adjusted for age, gender, heart failure, hypertension, diabetes mellitus, vascular disease, chronic kidney disease, and hyperlipidemia.

Table II. Multivariate Cox Regression Proportional Hazards Model for Mortality Between Treatment and Nontreatment Groups

| Variable | Adjusted HR* | 95% CI |
|----------|--------------|--------|
| Without treatment | 1.00 | - |
| With treatment | 0.21* | 0.16-0.28 |
| Treatment with Warfarin only | 0.28* | 0.15-0.52 |
| Treatment with Aspirin + Warfarin both | 0.21* | 0.15-0.30 |
| Treatment with Aspirin only | 0.22* | 0.16-0.29 |
| Age at entry, years | | |
| 50-64 | 1.00 | - |
| 65-74 | 2.08* | 1.28-3.36 |
| ≥ 75 | 3.10* | 1.47-6.55 |
| Gender | | |
| Female | 1.00 | - |
| Male | 1.26 | 0.95-1.68 |
| Comorbidity | | |
| Hypertension | 0.61 | 0.36-1.04 |
| Diabetes mellitus | 0.64 | 0.26-1.55 |
| Hyperlipidemia | 0.64 | 0.38-1.06 |
| Congestive heart failure (CHF) | 1.18 | 0.66-2.11 |
| Chronic kidney disease (CKD) | 1.72* | 1.08-2.75 |
| Vascular disease | 1.81* | 1.22-2.68 |

Although we could not precisely identify the truly low-risk patients, this scoring system has the advantages of being neat, easy to remember, and clinically practical. It is widely used among first-line medical personnel. According to our findings, we recommend using a practical algorithm to avoid undertreating patients with AF who are at the gray zone of risk. If the CHADS2 score is 0 (observed in only 6.4% to 7% of gray zone patients in our study), further evaluation based on the CHADS2-VASc scores is required for decision-making. Only a CHADS2-VASc score ≥ 5 is required for decision-making. Only a CHADS2-VASc score ≥ 5 is required for decision-making.
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Figure 2. A: Kaplan-Meier survival curves for mortality in the treatment and nontreatment groups. B: Kaplan-Meier survival curves for mortality after adjustment for the time lag between the treatment and nontreatment groups.

VASc score ≥ 2 for men and ≥ 3 for women is associated with a definite recommendation for anticoagulant therapy.22)

Anticoagulant therapy is acknowledged to be of major importance for preventing stroke in AF, and it is the most effective treatment for patients with a high stroke risk. However, anticoagulant therapy continues to be underused for patients with AF globally, particularly in Asia.23) In Hong Kong, 45% of patients with AF were prescribed only acetylsalicylic acid (ASA), 31% received oral anticoagulants, and 24% had no treatment.24) In Taiwan, only 24.7% received guideline-based therapy, 50.6% of high-risk patients took ASA, and 29% took no medications.25) Although gaps exist between the guideline and clinical practice, antiplatelet and anticoagulant drugs are both related to improved prognosis in patients with AF.26) In our observational study, both antiplatelet and anticoagulant therapies could improve survival in not truly low-risk patients with AF.

Aspirin has a proven role in the prevention of further vascular events after a stroke or TIA. Aspirin is less efficacious than warfarin in patients with AF, reducing the risk of stroke by approximately 20%.27) In addition, no significant differences were observed between aspirin and clopidogrel for the composite endpoints of stroke, myocardial infarction, and vascular death.28) According to the Hypertension Optimal Therapy study,29 aspirin reduced the occurrence of myocardial infarction but increased major hemorrhage, and it did not reduce all-cause mortality or cardiovascular mortality. Although the precise pathophysiology of mortality reduction was unclear, similar benefits were observed in patients with heart failure30 who received antiplatelet and anticoagulant agents. However, the benefits of aspirin use on vascular death cannot be ignored. The role of aspirin in reducing long-term mortality in patients with AF needs more evidence.

Warfarin can prevent recurrent stroke in patients with nonrheumatic AF.31) Results of several randomized clinical trials of antithrombotic therapies have demonstrated that, compared with a placebo, adjusted-dose warfarin reduces first or recurrent stroke by approximately 60%. The rationale is that the prescription of an anticoagulant is independently associated with a decreased risk of death or stroke among patients with AF and CHADS2 score = 1.32) In patients with AF with a CHADS2 score = 1, warfarin was more effective than aspirin in preventing ischemic stroke, without increasing the incidence of major bleeding complications. However, the incidence of minor bleeding was higher in the warfarin group than in the aspirin group.33) In the real world, the risk of bleeding complications after taking warfarin remains a concern. Hence, a sizable portion of elderly patients (aged ≥ 75 years) who were not taking anticoagulants had a borderline risk score. Elderly and female patients were less likely to receive thromboembolic prophylaxis.33) The undertreatment of elderly patients may partially explain the higher mortality observed in this subpopulation. Regarding stroke prevention, warfarin therapy in patients with AF and ischemic stroke was associated with a reduced risk of death, without an increased risk of fatal hemorrhagic stroke.34) Of the patients in whom AF was diagnosed prior to the index stroke, only approximately 23% received anticoagulation according to guideline recommendations.35) Our findings also reflect the reality of undertreatment of elderly patients (only 11.5% of AF patients aged ≥ 75 years received medication), resulting in high mortality.

Study limitations: First, the database lacks details of smoking history, family history, body mass index, and other relevant comorbidities, and especially, the history of hemorrhage events and complications after taking medicine, or if the patient received other treatments for AF such as catheter ablation or anti-arrhythmic drugs. Therefore, caution must be exercised in interpreting our data. Second, because the risk factors and diagnosis were retrospectively extracted from the database according to ICD-9-CM codes, a prospectively randomized control trial needs to be undertaken in a population with AF in the gray zone of stroke risk. Third, all cases in this study
were collected from claim datasets of NHIL and the diagnoses were based on physician reports only; therefore, it is unclear how our findings can be generalized to patients in different areas. Fourth, since this study was not a randomized clinical trial, we cannot conclude that antithrombotic therapy can reduce mortality. Further randomized clinical trials are needed to confirm our results.

Conclusion

In conclusion, our study findings reveal the necessity of antithrombotic treatment (anticoagulant and/or antiplatelet) in patients with AF with a CHADS2 score ≥ 1 and a CHA2DS2-VASc score ≥ 2. Further investigations are needed to observe whether antithrombotic treatments have any benefits for patients with AF with a CHA2DS2-VASc score < 2.

Disclosures

Conflicts of interest: The authors have no conflicts of interest that are directly relevant to the content of this article.

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