Research Article

Clinical characteristics and one year outcomes in Chinese atrial fibrillation patients with stable coronary artery disease: a population-based study

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Abstract

Background Atrial fibrillation (AF) and coronary artery disease (CAD) often coexist, however, the clinical characteristics and the impact of stable CAD on the outcomes in Chinese patients with AF has not been well understood. Methods Consecutive AF patients in 20 hospitals in China from November 2008 to October 2011 were enrolled. The primary endpoints included 1-year all-cause mortality, stroke, non-central nervous system (non-CNS) embolism, and major bleeding. Results A total of 1947 AF patients were analyzed, of whom 40.5% had stable CAD. The mean CHADS2 scores in CAD patients were significantly higher than that of non-CAD patients (2.4 ± 1.4 vs. 1.4 ± 1.2, \( P < 0.001 \)). During follow-up period, warfarin use is low in both groups, with relatively higher proportion in non-CAD patients compared with CAD patients (22.3% vs. 10.7%, \( P < 0.001 \)). Compared with non-CAD patients, CAD patients had higher one-year all-cause mortality (16.8% vs. 12.9%, \( P = 0.017 \)) and incidence of stroke (9.0% vs. 6.4%, \( P = 0.030 \)), while the non-CNS embolism and major bleeding rates were comparable between the two groups. After multivariate adjustment, stable CAD was independently associated with increased risk of 1-year all-cause mortality (HR = 1.35, 95% CI: 1.01–1.80, \( P = 0.040 \)), but not associated with stroke (HR = 1.07, 95% CI: 0.72–1.58, \( P = 0.736 \)). Conclusions Stable CAD was prevalent in Chinese AF patients and was independently associated with increased risk of 1-year all-cause mortality. Chinese AF patients with stable CAD received inadequate antithrombotic therapy and this grim status of antithrombotic therapy needed to be improved urgently.

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Keywords: Antithrombotic therapy; Atrial fibrillation; CHADS2 score; Stable coronary artery disease

1 Introduction

Atrial fibrillation (AF) is the commonest sustained disorder of cardiac rhythm, occurring in 1%–2% of the general population.\(^{[1]}\) The incidence of AF increases with age and an estimated 8 million people are affected in China.\(^{[2]}\) AF is associated with increased morbidity, especially stroke and heart failure, and increased mortality, resulting in serious health threat and costly health burden.\(^{[3]}\)

Coronary artery disease (CAD) and AF often coexist and interact with each other. On the one hand, ischemic myocardium, especially in the setting of acute ischemia, is predisposed to AF;\(^{[4]}\) on the other hand, coexistence of AF and CAD not only make the antithrombotic treatment strategies complicated,\(^{[5]}\) but also adversely influence the outcomes.\(^{[6–8]}\)

As is known, one of main characteristics of Chinese AF patients is the low rate of anticoagulant therapy compared with that of patients in Western countries.\(^{[2]}\) However, the clinical characteristics and outcomes in Chinese AF patients with stable CAD are not well understood. Accordingly, the objectives of the present study were to assess (1) the clinical characteristics of Chinese AF patients with stable CAD; (2) the medical therapy, especially antithrombotic therapies (based on CHADS2 risk stratification); and (3) the impact of stable CAD on the 1-year outcomes in Chinese AF patients.

2 Methods

2.1 Study protocol and patient population

This AF registry was a prospective, observational, multi-
center study of patients who presented to the emergency department with AF. A total of 20 medical centers in China participated in this registry between November 2008 and October 2011. Registry sites were selected to represent different levels of medical care (academic and nonacademic; general and specialized; and urban and rural). AF was diagnosed by ECG, Holter monitor, rhythm strip or pacemaker electrogram at the time of patient visits, either as the primary reason for their visit or as a secondary diagnosis.

The definitions of stable CAD were as following: (1) those having stable angina pectoris or other symptoms associated with CAD; (2) those previously symptomatic with known obstructive or non-obstructive CAD, but become asymptomatic with treatment; and (3) those who had a history of acute coronary syndrome (including ST segment elevation acute myocardial infarction, non-ST segment elevation acute myocardial infarction, unstable angina), but had 12 months from an acute coronary event. Those who presented with acute coronary syndrome were excluded.

The study coordinator or the physician used standardized data collection forms to record patient demographics, medical history, clinical presentation, electrocardiogram findings, use of medications and the outcomes during the follow-up period. The central administrative office of the study is located at the Fuwai Hospital (Beijing, China) and Study protocols were approved by the appropriate institutional review boards of Fuwai hospital and complied with the Declaration of Helsinki. The study investigators received the necessary approvals from their local hospital ethics or institutional review boards, and informed consent was obtained from all patients.

2.2 Follow-up and outcomes

Clinical follow-up was obtained for all patients via telephone, clinic visit or medical record procurement approximately 12 months after consenting to the study. The primary endpoints included: (1) all-cause mortality; (2) stroke; (3) non-central nervous system (non-CNS) embolism; and (4) major bleeding. All-cause mortality included cardiovascular death and non-cardiovascular death. Stroke was defined as the sudden onset of a focal neurologic deficit in a location consistent with the territory of a major cerebral artery and was categorized as ischemic, hemorrhagic or unspecified. Non-CNS embolism was defined as an acute vascular occlusion of an extremity or organ and was documented by imaging, surgery or autopsy. Major bleeding was defined as: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as the intra-cranial or pericardial regions, or intra muscular bleeding with compartment syndrome, bleeding that led to the transfusion of two or more units of whole blood or red cells and/or bleeding that caused a decline in the hemoglobin level of 20 g/L (1.24 mmol/L) or more.

2.3 Statistical analysis

Continuous variables are presented as mean ± SD or median with interquartile range. Categorical variables are presented as frequencies (percentages) as appropriate. Comparisons between groups were performed using the Chi-square test for binary factors and the Kruskal-Wallis equality-of-populations rank test for continuous variables. Kaplan-Meier curves were computed for all-cause mortality and stroke, and the log-rank test was used to test the differences in the unadjusted survival curves. Multivariate analysis of the effect of stable CAD on all-cause mortality and stroke were performed using a Cox proportional hazards model. Hazard ratios (HRs) and 95% confidence intervals (CIs) are presented. In multivariable analyses, age, sex, stable CAD, medical histories, and medications were included for adjustment. A probability value of \( P < 0.05 \) was considered statistically significant. All tests were two-sided. The software package SPSS 19.0 (IBM Corporation, New York, NY, USA) was used for statistical analysis.

3 Results

A total of 2016 AF patients were enrolled in this AF registry and 69 patients with AF and acute coronary syndrome at first presentation were excluded. The remaining 1947 patients were divided into two groups based on the presence or absence of stable CAD.

3.1 Baseline characteristics of the study population

Table 1 shows the baseline characteristics in patients with and without stable CAD. Of the 1947 AF patients included in this study, 788 (40.5%) had stable CAD. Patients with CAD were more likely to be older, male, and to have higher admission blood pressure and higher body mass index (BMI), but had lower admission heart rate (all \( P < 0.05 \)). They were also more likely to have concomitant hypertension, diabetes mellitus, heart failure, chronic obstructive pulmonary disease (COPD), and history of stroke/transient ischemic attack (TIA), but have less valvular disease (all \( P < 0.001 \)). The mean CHADS2 (Congestive heart failure, Hypertension, Age, Diabetes, Stroke/transient ischemic attack) scores in CAD patients was significantly higher than that of non-CAD patients (2.4 ± 1.4 vs. 1.4 ± 1.2; \( P < 0.001 \)), in which the percentage of patients with CHADS2 ≥ 2 in CAD patients was significantly higher than that of patients without CAD while the portion of patients with CHADS2 =
0 or 1 in CAD patients was less than in non-CAD patients ($P < 0.001$).

Table 2 shows the treatment during follow-up period. Compared with non-CAD patients, patients with stable CAD received more evidence-based secondary prevention therapies such as β-blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and statins (all $P < 0.05$). With respect to antithrombotic therapy, aspirin was the main antithrombotic drug adopted by 67.3% of CAD patients and 45.0% of non-CAD patients ($P < 0.001$). Small percentage of patients received clopidogrel in both CAD (10.7%) and non-CAD patients (2.5%) ($P < 0.001$). Moreover, the use of warfarin for anticoagulation is also low in both groups, with relatively higher proportion in non-CAD patients compared with CAD patients (22.3% vs. 10.7%, $P < 0.001$).

### 3.2 Antithrombotic therapy based on CHADS2 scores

Figure 1 displays the antithrombotic therapy strategies according to CHADS2 scores. It was shown more than half of AF patients with stable CAD received aspirin, regardless

| Treatment | CAD, $n = 788$ | Non-CAD, $n = 1159$ | $P$-value |
|-----------|----------------|---------------------|-----------|
| β-blocker | 378 (48.0%) | 466 (40.2%) | 0.001 |
| Digoxin | 227 (28.8%) | 376 (32.4%) | 0.089 |
| CCB | 202 (25.6%) | 242 (20.9%) | 0.014 |
| Amiodarone | 76 (9.6%) | 108 (9.3%) | 0.813 |
| Propafenone | 14 (1.8%) | 40 (3.5%) | 0.034 |
| Diuretic | 331 (42.0%) | 417 (36.0%) | 0.007 |
| ACEI | 220 (27.9%) | 224 (19.3%) | < 0.001 |
| ARB | 179 (22.7%) | 127 (11.0%) | < 0.001 |
| Statins | 330 (41.9%) | 112 (9.7%) | < 0.001 |

Data are presented as mean ± SD or n (%). ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; INR: international normalized ratio.

Figure 1. Antithrombotic therapy strategies based on CHADS2 score. (A): Antithrombotic therapy strategies based on CHADS2 score in patients with stable CAD; (B): antithrombotic therapy strategies based on CHADS2 score in patients with stable non-CAD. CAD: coronary artery disease; CHADS2: congestive heart failure, hypertension, age > 75 years, diabetes, prior stroke/transient ischemic attack; COPD: chronic obstructive pulmonary disease; TIA: transient ischemic attack.

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of the CHADS2 scores. When the CHADS2 score ≥ 2, 67.4% of patients still received aspirin while only 10.7% of patients received warfarin for antithrombotic therapy (Figure 1A). In non-CAD patients, similar trends were found, however, the percentage of patients with warfarin was relatively higher than in CAD patients (Figure 1B). Moreover, 16.0% of CAD patients and 21.8% of non-CAD patients with CHADS2 score = 0 received warfarin for antithrombotic therapy.

Figure 2 further showed the detailed antithrombotic therapy strategies. In patients with stable CAD, 56.4% of patients used aspirin or clopidogrel alone, 7.9% with double anti-platelet therapy (DAPT), 7.0% with warfarin, 2.9% with warfarin plus aspirin (or clopidogrel), and 0.3% with triple antithrombotic therapy. Similar trends were also found in patients without CAD. Notably, 22.8% of CAD patients and 41.0% of non-CAD patients did not received any antithrombotic drugs.

3.3 One-year outcomes

Figure 3 shows the 1-year outcomes in AF patients with or without stable CAD. All-cause mortality was higher in CAD patients compared with non-CAD patients (16.8% vs. 12.9%; P = 0.019). The incidence of stroke was also higher in CAD patients than in non-CAD patients (9.0% vs. 6.4%; P = 0.030). However, the non-CNS embolism (1.1% vs. 0.5%; P = 0.122) and major bleeding rates (0.9% vs. 1.6%; P = 0.201) were comparable between the two groups.

Figure 4 shows the Kaplan-Meier curves in patients with or without stable CAD. The cumulative survival in CAD patients were significantly lower than in non-CAD patients (Log rank, P = 0.017, Figure 4A). The cumulative freedom from stroke in CAD patients were also significantly lower than in non-CAD patients (Log rank, P = 0.031, Figure 4B).
Table 3 lists the predictors of 1-year all-cause mortality and stroke in patients with AF. After adjusting for baseline characteristics, medications during follow-up by Cox regression analysis, stable CAD was associated with a higher risk of 1-year all-cause mortality (HR = 1.35, 95% CI: 1.01–1.80; P = 0.040). In addition, age, heart rate, hypertension, COPD, and CHADS2 score were also positively correlated with all-cause mortality, whereas BMI and warfarin use were protectors of 1-year all-cause mortality. However, after multivariate adjustment, stable CAD was not independently associated with stroke (HR = 1.07, 95% CI: 0.72–1.58; P = 0.736).

4 Discussion

The data from our study demonstrates that, in Chinese AF patients: (1) stable CAD is common among patients with AF and is associated with more co-morbidities; (2) the antithrombotic therapy was nonstandard and the percentage of AF patients on oral anticoagulation therapy was low, despite the recommendations given in published guidelines; and (3) patients with AF and stable CAD were at higher risk of adverse outcomes and stable CAD was strongly associated with a higher risk of 1-year mortality.

This study is the first nationwide survey of AF registry patients who presented to the emergency department in a true clinical practice setting in China. In our study, over 40% of AF patients had concomitant CAD, consistent with previous reports.[9–11] These patients were more likely to be older and to have more co-morbidities such as heart failure, stroke/TIA and diabetes mellitus, as previously reported.[12,13]

Most previous studies mainly focused on AF after acute coronary syndrome and demonstrated AF adversely influences the outcome in patients with acute coronary syndrome.[14–17] However, studies concerned with the clinical characteristics and outcomes in patients with AF and stable CAD are relatively sparse. Our study was the first to evaluate the clinical profiles and prognosis in Chinese AF patients with stable CAD and to demonstrate nonstandard antithrombotic therapy and low oral anticoagulation therapy as well as the increased risk of 1-year mortality in Chinese AF patients with stable CAD.

There are differences in the pathogenesis of thrombosis between AF and CAD. The major complications in patients with AF are stroke and systemic embolism while the major clinical events associated with CAD are acute coronary syndrome. Therefore, the antithrombotic therapy strategies are also different. Oral anticoagulation is appropriate for patients with moderate to high risk of AF, while anti-platelet therapy is the standard management for CAD to reduce the risk of coronary events. However, in patients with AF and CAD, the choice of optimal antithrombotic therapy to prevent both thromboembolic and cardiac events is often challenging because the potential benefit of combination therapy may face an increased risk of bleeding, thus making the treatment contentious.

Until now, the appropriate antithrombotic regimen in stable CAD in the presence of AF is unclear due to the lack of randomized clinical trials (RCTs). Current guideline recommendations have been mainly based on findings from retrospective studies, observational data, or non-randomized trials. For patients with stable CAD and AF at low risk of stroke (CHADS2 = 0), aspirin alone is recommended and in patients with moderate to high risk of stroke (CHADS2 ≥ 1 or CHA2DS2-VASc ≥ 1), oral anticoagulation is recommended.[18,19] Our population reflects a “real-world” scenario for the applicability of current AF guidelines. Our study shows that most of AF patients did not receive guideline-recommended antithrombotic therapy. The major shortcoming of antithrombotic therapy in our study population was the low anticoagulation rate. The percentage of patients who received anticoagulation therapy was small in the entire cohort and even smaller in patients with stable CAD. Instead, aspirin, which has been confirmed to have limited preventive effect on thrombus,[20] was prevalent in our study. Being afraid of bleeding, the need for frequent monitoring of the international normalized ratio, and exces-
sive interaction between warfarin and other medications or foods might result in low use of warfarin. Moreover, if patients with stable CAD received aspirin or clopidogrel, or both, and for the sake of safety, clinicians might hesitate to select oral anticoagulation instead of anti-platelet therapy even if the patients were at moderate to high risk of stroke. In addition to the under-treatment status, a portion of patients were given over-treatment, such as low risk of stroke (CHADS$_2$ = 0) with warfarin, or some receiving both anticoagulation and anti-platelet therapy. More seriously, 22.8% of CAD patients and 41.0% of non-CAD patients did not receive any antithrombotic therapy. This is the current grim status of antithrombotic therapy in Chinese AF patients. It is expected that more AF patients would receive standard antithrombotic therapy by means of propaganda and education for both clinicians and patients to diminish the gap between guidelines for AF and everyday clinical practice. Moreover, it is also anticipated new oral anticoagulants characterized by favorable safety, effectiveness, and convenience would be widely available in China.

Our study also demonstrated that stable CAD was independently associated with increased risk of 1-year all-cause mortality. The mechanism is not well understood. However, as is mentioned above, AF patients with stable CAD usually had more co-morbidities and therefore, were at high risk of poor outcomes. Moreover, although these patients had stable atherosclerotic lesions at baseline, some might undergo acute cardiovascular events during follow-up period, which increased the risk of poor outcomes. In addition, low antithrombotic therapy rate, especially low anticoagulation rate, might result in increased risk of stroke and long-term mortality because previous studies and our study shows that warfarin use was associated with reduced risk of all-cause mortality.[21] Therefore, it is of utmost importance to improve the current grim status of antithrombotic therapy so as to improve the prognosis in Chinese AF patients.

In current guidelines for the management of AF, vascular disease (prior myocardial infarction, peripheral arterial disease, or aortic plaque) is a risk factor of stroke.[22] Although the incidence of stroke in patients with stable CAD was higher than that of non-CAD patients in our study, after multivariate adjustment, stable CAD was not independently associated with the occurrence of stroke. A possible interpretation may be that stable atherosclerotic lesion is associated with relatively low risk of stroke. Moreover, the relatively short follow-up time (1-year) might not be long enough to detect the obvious impact of stable CAD on the occurrence of stroke. In addition, statin use in this group of patients was more widely prescribed, which might reduce the incidence of stroke because studies have shown statin use is associated with reduced risk of stroke.[23–25] Therefore, more studies are needed to confirm the association of stable atherosclerotic lesion and stroke.

Some limitations in our study should be considered. First, our data regarding the patients’ history of CAD were collected only at the baseline visit and the information of subsequent events during follow-up period was unavailable. Secondly, the CHA$_2$DS$_2$-VASc score is a more comprehensive risk factor-based approach to calculate stroke risk in patients with AF; thus, it is especially indicated in low- and intermediate-risk categories. However, we did not collect data about the history of peripheral vascular disease and were not able to calculate the CHA$_2$DS$_2$-VASc score in this survey. Meanwhile, we did not have data on the risk of bleeding. Thus, we could not draw any definite conclusions about anticoagulation management or assessment of bleeding risk (i.e., HAS-BLED score). Third, the details of the atherosclerotic lesion, cardiac structure and function evaluated by coronary angiography and echocardiography were lacking. In addition, patients were enrolled in the warfarin era before new oral anticoagulants were widely used in China and whether the epidemiologic feature of patients with AF changed significantly in recent years deserves further study. Finally, although our study demonstrated stable CAD was independently associated with increased risk of all-cause mortality, the follow-up time is relatively short and therefore, a long-term follow-up was needed to evaluate the association of stable CAD with the cardiovascular events in patients with AF. Therefore, more studies are needed to confirm our findings.

In conclusion, stable CAD was prevalent in Chinese AF patients and was independently associated with increased risk of 1-year all-cause mortality. Chinese AF patients with stable CAD received inadequate antithrombotic therapy and this grim status of antithrombotic therapy needed to be improved urgently.

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