

Off-label Non-vitamin K Antagonist Oral Anticoagulants Does Not Decrease the Stroke Risk of Atrial Fibrillation Patients in East China

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Research

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Abstract

Background: For anticoagulation therapy of atrial fibrillation (AF) in east Asia, some off-label dose, so called “Asian Dose” of non-vitamin K antagonist oral anticoagulants (NOACs) was used concerning on the bleeding risks in these patients, such as low-dose rivaroxaban (10-15 mg once daily) or dabigatran (110-150 mg once daily). However, the efficacy of the off-label dose of NOACs remains controversial.

Methods: We conducted a retrospective cohort study to compared the efficacy and safety among patients with AF in three groups: patients with the off-label dose of NOACs treatment (OFL group, dabigatran 110 mg once daily or rivaroxaban under 20 mg daily), patients with the standard dose of anti-coagulation therapy (SAG group, dabigatran 110 mg twice daily or rivaroxaban 20 mg once daily, or warfarin with international normalized ratio (INR) 2-3), and patients without non-coagulation treatment (NCG group) in east China.

Results: A total of 296 patients were recruited in our study. Compared to patients in SAG group, patients in OFL group had higher risk in stroke and thromboembolism events ($P=0.000$). The risk of other events including major bleeding ($P=0.597$) was comparable in these two groups, while there was no significant difference in all-cause mortality, which were both dramatically lower than NAG group (0.52, $P=0.000$).

Conclusions: Collectively, our results demonstrate that “Asian dose” of NOACs indeed can not bring much benefit for AF patients in east China.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia worldwide[1, 2], while anti-coagulation therapy remains the main strategy for AF including vitamin K antagonists (VKAs) and non-vitamin K antagonist oral anticoagulants (NOACs)[3]. Some studies have reported that the efficacy of NOACs are superior than VKAs among AF patients in East Asia[4].

Because of a greater risk for anti-coagulation related intracranial hemorrhage in east Asia, there is a compromised dosage of NOACs concerning the bleeding risk for anti-coagulation therapy[5]. Patients are usually given a so called “Asian dose” of NOACs such as low-dose rivaroxaban (10–15 mg once daily) or dabigatran (110–150 mg once daily) in China[6, 7]. Several studies have demonstrated that Asian dose brings much benefit for AF patients in East Asian due to the lower bleeding risk[4, 8]. However, the latest European Society of Cardiology (ESC) guideline indicates that reduced dose may be only favorable for patients with renal disease for rivaroxaban and apixaban[9]. The benefit of “Asian dose” was still controversial. Here, we set out this observational study to investigate whether the “Asian dose” of NOACs really exists for stroke prevention in AF patients in China.

Subjects And Methods

Patients and study design

This was a retrospective study of prospectively obtained data from patients seen between January 2015 and December 2015 at a tertiary referral center in the East of China. Patients who diagnosed as Atrial fibrillation (AF) with an estimated glomerular filtration rate ≥ 30 ml/min/1.73 m² were recruited. The diagnosis of AF was based on the ESC guideline that at least 30 seconds electrocardiogram or 24 h-Holter before or during hospitalization. Patients who uses warfarin irregularly or with INR value < 2 were excluded. Finally, a total of 342 patients were recruited in this study. Then, according to the anti-coagulation therapy, patients were divided into three groups including standard anti-coagulation (SAG) group, off-label (OFL) group and non-coagulation (NCG) group. Patients in SAG group received standard dosage of anti-coagulation therapy, including rivaroxaban 20 mg once daily or dabigatran 110 mg/150 mg twice daily, or warfarin with INR 2–3. Patients in OFL group received rivaioxaban < 20 mg daily or dabigatran 110 mg/150 mg once daily. Patients without anti-coagulation therapy were classified into NAG group. Patients were followed up every 6 months up to 5 years. All clinical events during follow-up including stroke and other thromboembolism events, acute coronary syndrome, major bleeding, all-cause mortality and re-hospitalization were collected.

Statistical analyses

All analyses were carried out using SPSS 24.0. Descriptive statistics were used to evaluate patient related secondary objectives. For patient characteristics, two-sided Student's t-test, Chi square test, and Fisher's exact tests were utilized as appropriate. Comorbid conditions and responsible physician type were analyzed using Chi square test, and concomitant medication use was analyzed using Fisher's exact test. All statistical tests were two-sided and a p-value of less than or equal to 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 342 patients with AF were included into this study, 296 of which were regularly followed up while 46 were missed because of incorrect contact information. There were 148 patients in NAG group, 37 patients in OFL group and 111 patients in SAG group, respectively. The baseline characteristics of these three groups were summarized in Table 1. The CHA₂DS₂-VASc score of the NAG group, OFL group and SAG group were 3.6 ± 1.8 , 3.7 ± 1.7 , 3.5 ± 1.7 , separately. Compared to OFL group (71 ± 10) and SAG group (69 ± 13), the age in NAG group was higher (73 ± 12). Unexpectedly, anti-platelet therapy was more common among patients in NAG group (49% in NAG to 35% in OFL and 10% in SAG).

Figure 1 shows the anti-coagulation drugs used in OFL group (Fig. 1a) and SAG group (Fig. 1b). Most of the OFL group used rivaroxaban, while warfarin remained predominant in SAG group.

Table 1
The Baseline characteristics of these 342 patients

	NAG group	OFL group	SAG group	P value
Number of patients (n)	148	37	111	
Male (%)	48	57	59	0.331
Age	73 ± 12	71 ± 10	69 ± 13	0.036
Hypertension (%)	60	62	54	0.473
CHF (%)	17	22	30	0.074
DM (%)	31	38	20	0.114
Vascular disease (%)	31	30	20	0.114
Previous stroke/SE (%)	22	35	43	0.014
CHA ₂ DS ₂ -VASc score	3.6 ± 1.8	3.7 ± 1.7	3.5 ± 1.7	0.760
HAS-BLED score	2.6 ± 1.2	2.3 ± 1.3	2.0 ± 1.1	0.001
Anti-platelet therapy (%)	49	35	10	0.000
SAG = standard anti-coagulation group, OFL = off-label group, NCG = non-anticoagulation group, CHF = congestive heart failure, DM = diabetes mellitus, SE = systemic embolism				

Events during follow-up

We collected clinical events during our follow-up up to 5 years (Fig. 2). Compared to patients in SAG group, patients in OFL group had higher risk in stroke and thromboembolism events ($P = 0.000$). The risk of other events including major bleeding ($P = 0.597$) and re-hospitalization ($P = 0.213$) was similar in both groups, as well as the cardiovascular mortality ($P = 0.640$). Minor bleeding such as gingival bleeding and skin bleeding occurred more in SAG group. All adverse events were more common in NAG group except major bleeding.

As shown in Fig. 3, there was no significant difference on all-cause mortality between OFL and SAG (0.14 and 0.19, $P = 0.601$), while these two groups were dramatically lower than NAG group (0.52, $P = 0.000$).

As shown in Fig. 4, the total cardiovascular events and mortality rate were not significant different between OFL group and SAG group ($P = 0.863$), while both were better than NCG group ($P = 0.000$).

Subgroup analysis for anti-platelet therapy

There were 73 patients using anti-platelet drugs such as aspirin and clopidogrel in NCG group, 75 patients without any anti-thrombotic therapy. We compared the anti-platelet subgroup with OFL group (Table 2).

Off-label anti-coagulation therapy was not superior to prevent stroke or SE compared to anti-platelet therapy. The bleeding risk was higher in OFL group as well. Whereas, off-label anti-coagulation could decrease coronary events and all-cause mortality apparently.

Table 2
The compare between anti-platelet group and NCG

	Anti-platelet subgroup	OFL group	P value
Number of patients (n)	74	35	
Stroke/SE (%)	15	17	0.707
Major bleeding (%)	0	6	0.039
ACS and HF (%)	22	0	0.007
Re-hospitalization (%)	78	69	0.270
Total cardiovascular mortality (%)	36	14	0.018
All-cause mortality (%)	47	14	0.001
OFL = off-label group, SE = systemic embolism, ACS = acute coronary syndrome, HF = heart failure			

Discussion

AF causes severe economic burden and medical cost[10]. In east Asia, NOACs have been proved to reduce the burden of stroke and death compared to VKA[11]. Previous study have indicated that nonwhites as Asians with AF were at greater risk for anti-coagulation related intracranial hemorrhage (ICH)[5]. Therefore, some compromised dosage of NOACs are applied for the treatment of atrial fibrillation in east Asia, which is so called "Asian dose".

Evidence has showed the benefit of low dose rivaroxaban in east Asia[8, 12]. Low dose of NOACs have been proposed to decrease the risk of hemorrhage compared to standard dose of NOACs. However, Cheng. *et al* pointed out that off-label rivaroxaban was associated with an increased risk of ischemic stroke with 2.75 times[6]. The standard dose NOACs was associated with a relatively mild stroke in the patients compared to under-dosed NOACs[13]. The previous studies were similar to our study which showed a poor clinical benefit of off-label anti-coagulation. The thrombosis risk was significantly higher in OFL group compared to SAG group. However, the thrombosis risk in OFL group was even higher than NAG group. This might be partly because of the survival period was shorter in NAG group. In addition, our results indicated that Asian dose of anti-coagulation therapy indeed did not lead to a less bleeding risk compared to the standard anti-coagulation therapy. In our study, standard dose of NOACs is only related to slightly increased risk of gingival bleeding and skin bleeding.

Here, our results show that the CHA₂DS₂-VASc score among the groups were close. The proportion of previous stroke and SE history were higher in OFL and SAG group while the age was higher in NAG group.

This outcome is highly reasonable in clinic as the anti-thrombotic therapy are more active for stroke AF patients. The HAS-BLED score of NAG group was higher compared to other groups. That might be the reason why anti-coagulation therapy was not applied for these patients. For elder patients, anti-coagulation needs more prudent due to the higher bleeding risk as well. In addition, rivaroxaban is used more commonly benefit from its various off-label dosage (10/15/20 mg per tablet).

Collectly, our study demonstrate that off-label anti-coagulation therapy can increase the survival rate of AF patients without decreasing the risk of stroke. We supposed that the major reason may be the reduction of coronary events, which are similar to a previous study in China[8]. Low dose rivaroxaban could reduce thrombus formation and platelet-dependent thrombin generation in patients with coronary heart disease, which are the potential ischemic benefits[14]. However, off-label NOACs brought higher bleeding risk without any benefits on thromboembolic events risk.

There were several limitations in our study. The sample size was relatively small, which may due to the loss of follow-up. In addition, the study was an observational study. More evidence such as randomized clinical trail is needed.

Conclusion

Asian dose of anti-coagulation therapy can not decrease the stroke risk of AF patients in east China. For the prevention of stroke and SE, standard dose of NOACs should be more appropriate for Asian AF patients. More experimental studies are needed to be carry out in the future.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients have signed informed consent previously.

Consent for publication

Written informed consent for publication was obtained from all participants.

Availability of data and materials

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no conflicts of interest.

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Authors' contributions

J. Li and X.P. Luo designed research for this study; P. Zhou, R.C. Liu, Y.J. Yu, W. C, Y.Z. Ma, H.Y. Wang and M. Waresi collected samples and performed research; M. Wang analyzed data; P. Zhou and M. Wang wrote the manuscript.

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Figures

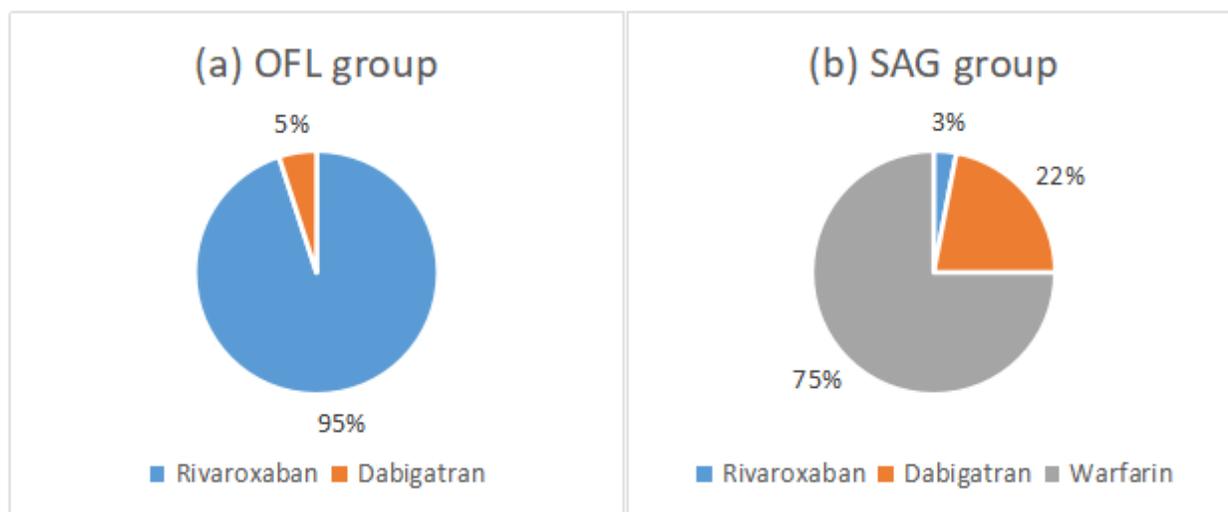


Figure 1

The anti-coagulation drugs used in OFL group (a) and SAG group (b)

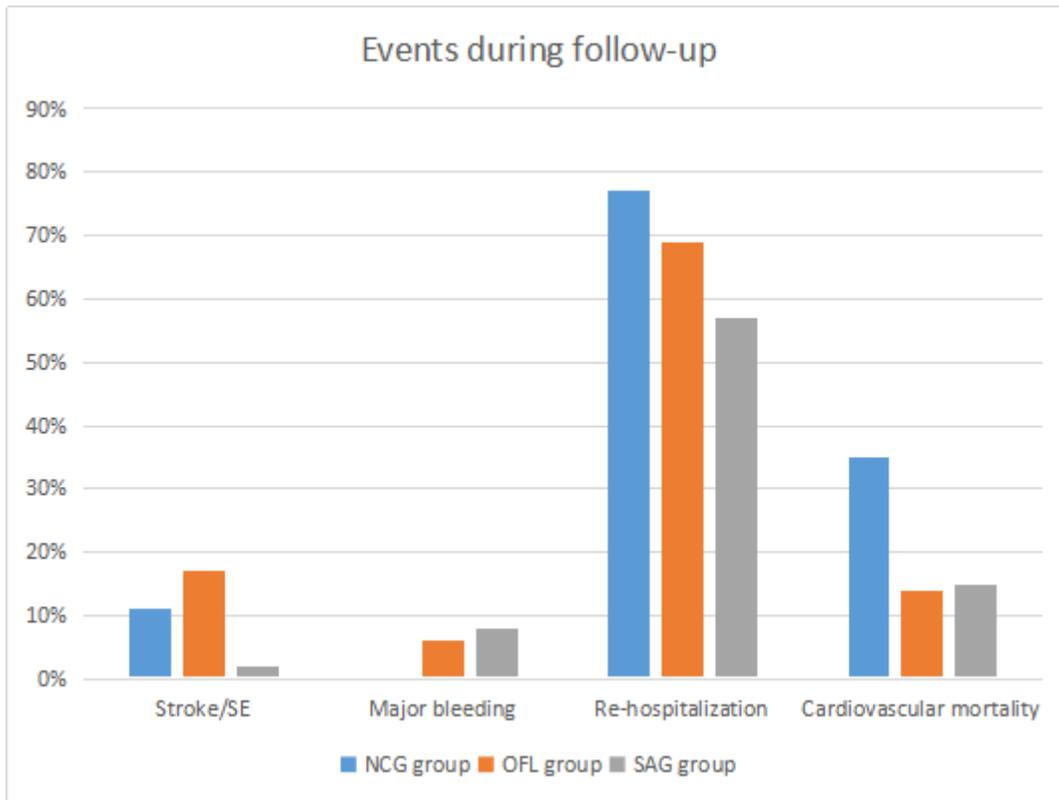


Figure 2

Clinical events during our follow-up up to 5 years

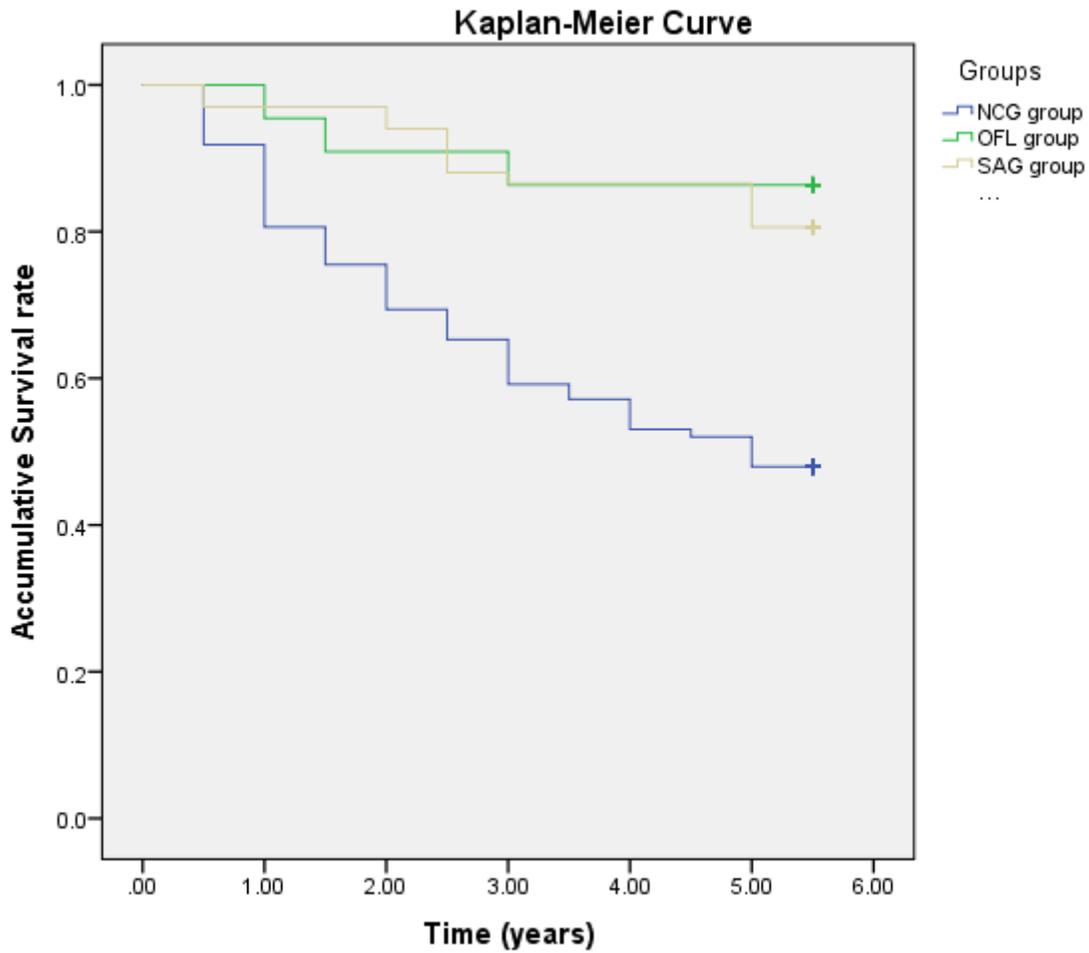


Figure 3

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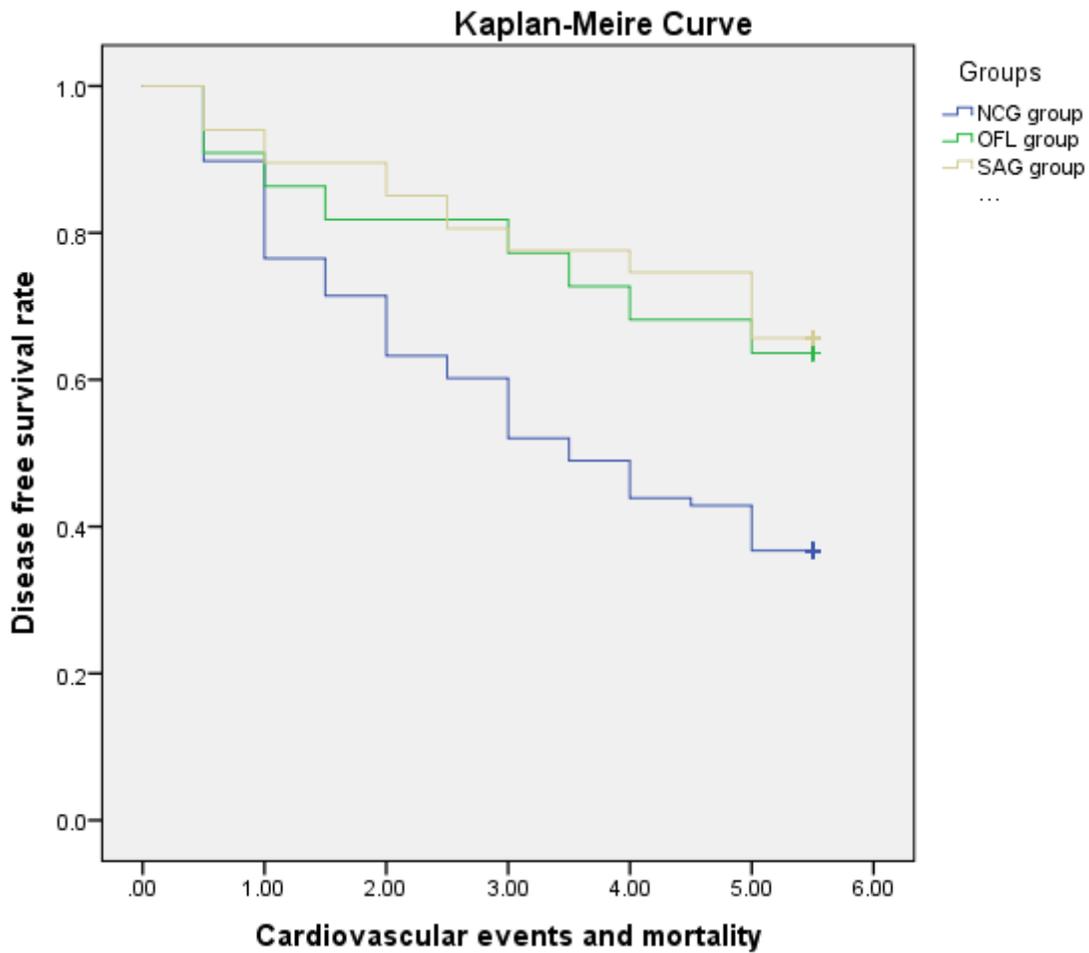


Figure 4

The total cardiovascular events and mortality rate were not significant different between OFL group and SAG group ($P=0.863$), while both were better than NCG group ($P=0.000$).