Do NOACs Improve Antithrombotic Therapy in Secondary Stroke Prevention in Nonvalvular Atrial Fibrillation?

Yi-Pin Lin, MD and Teng-Yeow Tan, MD

Abstract: Guidelines recommended oral anticoagulant (OAC) for ischemic stroke patients related to atrial fibrillation (AF). But, underprescription or underdose of warfarin was observed worldwide. We aimed to explore if the use of antithrombotic therapy in nonvalvular AF (NVAF) ischemic stroke patients improved after novel oral anticoagulants (NOACs) became available. Between January 2011 to December 2013, 360 acute ischemic stroke patients related to NVAF were recruited. Patients were categorized into 2 groups based on the date (July 2012) of NOACs’ availability. There were 184 patients recruited before July 2012, and whereas 176 patients after July 2012. Demographic data, interested factors, and the percentage of patient on OAC were compared.

One month after discharge, percentage of OAC utilization was significantly higher (29% versus 41%; P = 0.022) as well as effective anticoagulation (22.2% versus 80.6%; P < 0.001); warfarin utilization was significantly less (28.3% versus 11%; P < 0.001) after NOACs became available. Antiplatelet agent utilization was high in 2 groups (57% versus 52%; P = 0.36). Age (odds ratios [OR] 0.947; 95% confidence intervals [CI] 0.912–0.984; P = 0.05), Barthel index (OR 1.012; 95% CI 1.000–1.025; P = 0.05), and NOACs’ availability (OR 1.857; 95% CI 1.086–3.175; P = 0.024) were the significant factors affecting the use of OAC.

A higher percentage of NVAF ischemic stroke patients returning for their 1-month follow-up were treated with NOACs than with warfarin. The use of antithrombotic therapy improved after NOACs became available. But, the majority of the patients were still received antplatelet agent for emboli stroke prevention.

INTRODUCTION

Taiwan’s Health Department reported that cerebrovascular disease remained the top 3 leading causes of death in recent 10 years. Among the stroke population, approximately 15% are related to atrial fibrillation (AF).1 AF-related ischemic strokes are generally more disabling and more often fatal than other ischemic stroke subtypes, thus represents a major healthcare burden.2 Stroke prevention is central to the management of AF patients. Fortunately, clinical trials had showed that emboli events can be significantly reduced by oral anticoagulant (OAC) for those patients at moderate or high risk of emboli events.3–5 But, due to the disadvantages of warfarin, OAC utilization was suboptimal worldwide.6–7 Recently, meta-analysis comparing novel OACs (NOACs) with warfarin had demonstrated that NOACs to be at least noninferior to warfarin in the prevention of emboli events in patients with nonvalvular AF (NVAF) and more importantly associated with significantly lower rate of intracranial hemorrhage.8 Thus, it is assumed that the advent of NOACs would improve the use of OAC in NVAF patients. In this retrospective study, we tried to answer if the use of antithrombotic therapy in NVAF ischemic stroke patients improved after NOACs became available, as well as describe the factors associated the use of OACs in a real-world clinical practice.

PATIENTS AND METHODS

Study Population

This was a 1 center, retrospective medical chart review study. The study protocol was approved by the institutional ethics committee of Chang Gung Memorial Hospital, Taiwan. From the data of stroke center registry between January 2011 and December 2013, we recruited acute cardiogenic emboli ischemic stroke patients according to Trial of Org 10172 in Acute Stroke Treatment criteria.9 All patients had NVAF which was defined when there was absence of prosthetic mechanical heart valves or significant valve disease that warrant intervention. All patients were cared by neurologists during their hospitalization. Only patients who returned to neurologists’ outpatient clinic in the study hospital 1 month after discharge were enrolled.

To compare the status of OAC utilization before and after NOACs became available in this study population, patients were categorized into 2 groups, patients in or not in NOACs era based on the date (July 2012) of NOACs’ availability in the study hospital. Patients were also categorized into 2 groups, with and without OACs to explore factors significantly associated the use of OACs.

Demographic data including age, gender, length of stay in hospital, stroke risk factors, National Institutes of Health Stroke Scale (NIHSS) score at admission, Barthel index (BI) at discharge, modified Rankin scale (MRS) at discharge, type of antithrombotic agents, and past medical history were registered. CHA2DS2-VASc score for stroke risk stratification according to

Abbreviations: AF = atrial fibrillation, BI = Barthel index, INR = international normalized ratio, MRS = modified Rankin scale, NIHSS = National Institutes of Health Stroke Scale, NVAF = nonvalvular atrial fibrillation, OAC = oral anticoagulant, TTR = time in therapeutic range.

DOI: 10.1097/MD.0000000000001627

(Received: June 12, 2015; revised: August 24, 2015; accepted: August 26, 2015.
From the Division of Cerebrovascular Disease, Department of Neurology, Chang Gung Memorial Hospital, Kaohsiung (YPL, TTY); School of Medicine, Medical College, China Medical University, Taichung and Department of Neurology, Tainan Municipal An-Nan Hospital-China Medical University, Tainan (YPL), Taiwan.
Correspondence: Teng-Yeow Tan, Division of Cerebrovascular Disease, Department of Neurology, Chang Gung Memorial Hospital, Kaohsiung, Taiwan. No. 123, Dabi Road, NiaoSung District, Kaohsiung 833, Taiwan (e-mail: tengyeow@pchome.com.tw).
All authors have read and approved submission of the article. Y-PL and T-YeT contributed equally to this work.
The authors have no funding and conflicts of interest to disclose.
Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved. This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms. ISSN: 0025-7974

Publisher: C15
For patients not receiving OAC or any antithrombotic therapy, we reviewed the medical charts for the reasons of not prescribing antithrombotic therapy. Postulated reasons included gastrointestinal bleeding (active peptic ulcers or gastrointestinal tract bleeding), old cerebral hemorrhage, thrombocytopenia (platelet count < 100,000), anemia (hemoglobin < 10 g/dL or hemoglobin decreased > 2 g/dL during admission), gross hematuria, ischemic stroke with hemorrhagic transformation, and any ecchymosis.

**Statistical Analysis**

The data were analyzed by using SPSS 20.0 statistics software (SPSS Inc, Chicago, IL). We expressed the categorical data by number (n) and percentage (%). Continuous data were reported as mean and standard deviation. Nonparametric data were presented as median value and interquartile range (IQR). Chi-squared test was used for comparing categorical variables in 2 groups, and the independent-sample Student’s t-test for the continuous variables. Mann–Whitney U tests were performed to compare associations between variables measured on a nonparametric scale, including length of stay in hospital, NIHSS score, BI, MRS, and CHA2DS2VASc score. Logistic regression analyses were performed to estimate the odds ratios and CHA2DS2VASc score in 2 groups. Multivariable logistic regression analyses were performed to estimate the odds ratios along with 2-sided 95% confidence intervals for interested factors affecting the use of OAC. Multivariable logistic regression analysis was performed including all factors. A P-value of less than 0.05 was considered statistically significant.

**RESULTS**

During the study period, there were 405 NVAF ischemic stroke patients admitted to neurological ward, 24 patients died during their hospitalization, and 21 patients lost follow-up after discharge. In total, 360 patients fulfilled our inclusion criteria. A total of 184 patients comprised the group when only warfarin can be used and 176 patients were in NOACs era. 72% (259/360) of the patients had previously diagnosed NVAF and for those with CHA2DS2VASc score ≥ 2, only 8.8% (29/328) were given OAC and no patients had international normalized ratio (INR) within 2 to 3.

The demographic data of all subjects were summarized in Table 1. There were no statistically significant differences in age, gender, length of stay in hospital, NIHSS score, BI, MRS, and CHA2DS2VASc score in 2 groups.

Comparing the status of antithrombotic therapy 1 month after discharge, there was significantly less patients (14.1% versus 7.4%, P = 0.04) received no antithrombotic therapy in patients who were not in NOACs era. The majority of all subjects (57% versus 52%, P = 0.36) still received antiplatelet agent in 2 groups. For those who were giving OAC, there was significantly (29% versus 41%, P = 0.022) more patients in NOACs era and also more patients (22.2% versus 80.6%, P < 0.001) received effective therapy (INR 2–3) for those receiving warfarin and those with NOACs. The percentage of patients with warfarin was significantly less (28% versus 11%, P < 0.001) in patients who were in NOACs era. The majority of patients in NOACs era were prescribed NOAC (Table 2).

Univariate analysis showed that patients who received OACs were significantly associated with age, gender, length of stay in hospital, NIHSS, MRS, BI, CHA2DS2VASc score, NOACs availability, and diabetic mellitus (Table 3). Table 4 shows the results of multivariable logistic regression analyses.

### TABLE 1. Demographic Data of 360 NVAF Ischemic Stroke Patients

| Age, y | Patients Not in NOACs Era n = 184 | Patients in NOACs Era n = 176 | P Value |
|--------|----------------------------------|-------------------------------|---------|
| 74/+/-10 | 75/+/-10 | 0.651 |
| 154 (84%) | 142 (81%) | 0.455 |
| 97 (53%) | 97 (55%) | 0.648 |
| Gender | 107:77 | 113:63 | 0.239 |
| (male:female) | (58:42%:64:36%) | |
| Length of stay, d | 12.5 (6, 28) | 11.0 (6, 31) | 0.613 |
| NIHSS | 9 (5, 17) | 7 (3, 15) | 0.054 |
| Barthel index | 55 (10, 90) | 50 (10, 95) | 0.332 |
| MRS | 4 (1.75, 5) | 4 (1, 5) | 0.622 |
| CHA2DS2VASc | 4 (4, 6) | 5 (4, 6) | 0.789 |
| CHF (LVEF < 40%) | 9 (5%) | 3 (2%) | 0.092 |
| Hypertension | 151 (82%) | 149 (85%) | 0.509 |
| Diabetes mellitus | 50 (27%) | 62 (35%) | 0.099 |
| Ischemic stroke/TIA | 81 (44%) | 74 (42%) | 0.705 |
| History of vascular events | 22 (12%) | 17 (10%) | 0.483 |

CHF = congestive heart failure, CHA2DS2VASc = congestive heart failure, hypertension, age ≥ 75, diabetes mellitus, old ischemic stroke/TIA, peripheral occlusive vascular disease, age 65–74, and sex category (female). LVEF = left ventricular ejection fraction, MRS = modified Rankin Scale, NIHSS = National Institutes of Health Stroke Scale, NOAC = novel oral anticoagulant, TIA = transient ischemic attack.

Factors that were identified to be significantly associated with the use of OAC included NOACs’ availability, BI, and age.

For those patients not receiving OAC, 35% of the patient who were not in NOACs era and 41% in NOACs era, found no

### TABLE 2. Types of Antithrombotic Therapy 1 month After Discharge

| Patients Not in NOACs Era n = 184 | Patients in NOACs Era n = 176 | P Value |
|----------------------------------|-------------------------------|---------|
| Nil | 26 (14.1%) | 13 (7.4%) | 0.04 |
| Aspirin | 70 (38.0%) | 55 (31.3%) | 0.18 |
| Aggrenox | 1 (0.5%) | 1 (0.6%) | 1 |
| Clopidogrel | 31 (16.8%) | 31 (17.6%) | 0.85 |
| Cilostazol | 0 | 1 (0.6%) | 1 |
| Warfarin | 52 (28.3%) | 20 (11%) | <0.001 |
| Dabigatran | 0 | 36 (20.5%) | |
| Rivaroxaban | 0 | 15 (8.5%) | 1 |
| Aspirin + clopidogrel | 1 (0.5%) | 1 (0.6%) | 1 |
| Aspirin + warfarin | 2 (1.1%) | 0 | 1 |
| Clopidogrel + cilostazol | 1 (0.5%) | 1 (0.6%) | 1 |
| Aspirin + dipyridamole | 0 | 1 (0.6%) | 1 |
| Aspirin + dabigatran | 0 | 1 (0.6%) | 1 |
| Any antiplatelet agent | 104 (57%) | 91 (52%) | 0.36 |
| Any NOACs | 54 (29%) | 72 (41%) | 0.022 |
| Effective OACs | 12 (22.2%) | 58 (30.6%) | <0.001 |
| Warfarin (INR 2-3) | 11 (21.6%) | 6 (30%) | 0.45 |

OACs = oral anticoagulants.
Patients with ischemic stroke related to NVAF were almost 2-fold more likely to be given OAC and mainly NOACs. On the other hand, patients with older age and more severe stroke were less likely to receive OAC.

ESC guidelines recommend OAC using well-controlled adjusted dose vitamin K antagonists (eg, warfarin) or NOACs for patients with AF and stroke risk factor(s). The ESC guidelines also recommend the use of the CHA2DS2-VASc score for stroke risk assessment. Effective stroke prevention with OAC or NOACs can be offered to AF patients with ≥ 1 stroke risk factor(s). All subjects in our study were high risk for recurrent embolic ischemic stroke, therefore recommended using OAC. In NOACs era, 29% of the patients received warfarin but INR within 2 to 3 was only 21.6%. This mirrored the result of Taiwan Stroke Registry study, 28% of cardiogenic embolic stroke patients received warfarin after discharge. Three other Taiwan’s studies showed that the prescription rate of warfarin was even less, ranging from 11% to 25%, and I reported only 22.9% of patients received warfarin had INR 2 to 3. This situation was better in western countries but still suboptimal, one-third to one-half of candidates eligible for warfarin use left untreated. Similar to our study population (ischemic stroke/TIA), several studies reported that percentage of OAC treatment was below 60%. Data from the United States demonstrated that there were up to 80% patients spending most of their time in the sub- or supratherapeutic range.
been shown to be lower in Chinese versus White population to use herbal remedies which are common in Chinese.

Most of the patients received warfarin-only era during 2009 to 2011, warfarin was prescribed in 45% of AF patients, whereas the NOACs in 4.5% of patients overall. In our study, the percentage of OAC prescription was significantly higher in NOACs era. Most of our patients received NOACs instead of warfarin. This favorable change in OAC treatment was mainly due to the impact of the advent of NOACs. For all antithrombotic therapy, more than half of the subjects were prescribed with antiplatelet agents. Those not receiving OAC, 35% of the patient not in NOACs era and 41% in NOACs era found no reason for no OAC treatment. But, older age was the significant factor associated with not using OAC. Knowing that the efficacy of aspirin declines at aged > 70 years while the risk of bleeding increases, this observation was interesting. Studies have found that aged patients were less likely to receive antiplatelet therapy than younger patients.

A retrospective review of hospital admissions for ischemic stroke in patients with AF found that the percentage of patients receiving OAC treatment declined as age advanced, 75% of patients treated with OAC at aged <75 years and dropped to 33% when aged >85 years.

The efficacy of antiplatelet treatment crossed all aged patients with AF. Especially those with advanced age showed in a study after analyzing almost 9000 patients with AF, the benefit of stroke prevention by OAC was even more pronounced. Beyond considering advanced age as a contraindication to warfarin, fear of elderly patients to have more bleeding complications is a frequently cited reason why clinicians do not prescribe anticoagulant therapy to older patients. However, The Birmingham Atrial Fibrillation Treatment of the Aged trial demonstrated that there was no difference in major bleeding events comparing patients treated with warfarin and patients treated with aspirin while showing the superiority of warfarin over aspirin in reducing the risk of ischemic stroke in patients with AF aged >75 years.

In a recent review article done by Yates focused on NOACs for stroke prevention in older patients with AF had also concluded that NOACs are suitable alternatives to warfarin in preventing embolic events based on the benefits of these agents in this particular population. But, properties such as individual drug metabolism and route of elimination should be considered when older patients especially those with chronic kidney disease were given these agents. The reduction in stroke risk must be balanced against the increased risk of bleeding and currently there is no antidote existed to reverse the anticoagulant effect of NOACs.

Another significant factor associated with no OAC was stroke severity as measured by BI. This may be attributed to the consideration of the total dependency of daily activities, high risk of falling accidents, and tendency to bleed. Besides, previous clinical trials of stroke prevention in AF excluded patients with severe stroke, therefore effect and safety of OAC in this subgroup was not well understood. Considering our limited medical resources and the insurance reimbursement policy, these might partly explained why these patients were not giving OAC treatment.

Among the postulated reasons of not giving OAC, peptic ulcers or gastrointestinal tract bleeding comprised the majority followed by ischemic stroke with hemorrhagic transformation, anemia, history of old intracranial hemorrhage, gross hematuria, thrombocytopenia, and any ecchymosis. No significant difference was found but when comparing patients receiving only 1 antiplatelet agent and those with no antithrombotic therapy, patient with gastrointestinal bleeding and thrombocytopenia were likely to receive no treatment, in contrary, the percentage of unknown reason was only 5% in patients with no treatment compared to 44.6% in patients with antiplatelet agent. The results implied that doctors still considered antiplatelet agent was safer than OAC (either warfarin or NOACs) in this real-world clinical practice. Our observational data were similar to the recent report from England, 41% of the patients without reasons for not using warfarin when eligible.

There were limitations in our study. First, the results were from small numbers of subjects in a single hospital and medical center, and it may not apply to whole AF population in Taiwan. Second, we only discussed about anticoagulation therapy of secondary prevention for stroke, but not disclose the clinical practice of primary prevention in AF patients with a moderate to high risk of stroke. Third, some important issues such as the impact on clinical outcome or dropout rate between the users of warfarin and NOACs were not explored in the study, which warrants further follow-up.

CONCLUSIONS

NOACs improved the use of antithrombotic therapy in NVAF ischemic stroke patients for further embolic events prevention but age and stroke severity hindered the use of OAC. Although the percentage of patients with effective

when using warfarin. In our study, only about 30% of patients receiving warfarin had INR 2 to 3.

The low prescription rate of warfarin in clinical practice results from its many disadvantages, including unpredictable response, narrow therapeutic window requiring routine coagulation monitoring and therefore frequent dose adjustment, slow onset/offset of action, numerous drug–drug or drug–food interactions, warfarin resistance, and finally the concerns of bleeding complications. Demographic and genetic differences exist between Asian populations and other ethnic groups, which may affect the use and dosing of OAC. Data from 2 studies have shown East Asian populations to be more sensitive to warfarin than Indian and White populations.

Dosage of warfarin had been shown to be lower in Chinese versus White population to obtain same coagulation effect.

Warfarin may also interact with herbal remedies which are common in Chinese.

The incidence of intracranial hemorrhage was increased in patients of Asian ethnicity who receive warfarin compared with other ethnic groups. As a result, OACs are suboptimal used in this region. Recently, a simple score (SAMe-TT2R2) which has been validated can predict poor INR control within this region. The predicting factors, race which is nonwhite score 2 and then age was the significant factor associated with not using OAC. Although the percentage of patients with effective

pharmacologic advantages, such as rapid onset/offset of action, predictable pharmacokinetics, less drug interactions, and a wide therapeutic window thereby facilitating fixed dosing in adults.

The results of RE-LY, ROCKET-AF, ARISTOLE, and ENGAGE AF-TIMI 48 trials had proved that NOACs offered at least noninferior stroke protection as compared with warfarin and a significant reduction in intracranial hemorrhage.

The Global Anticoagulant Registry in the FIELD, an observational worldwide study on NVAF collected at the end of the warfarin-only era during 2009 to 2011, warfarin was prescribed in 45% of AF patients, whereas the NOACs in 4.5% of patients overall. In our study, the percentage of OAC prescription was significantly higher in NOACs era. Most of our patients received NOACs instead of warfarin. This favorable change in OAC treatment was mainly the impact of the advent of NOACs.

For all antithrombotic therapy, more than half of the subjects were prescribed with antiplatelet agents. Those not receiving OAC, 35% of the patient not in NOACs era and 41% in NOACs era found no reason for no OAC treatment. But, older age was the significant factor associated with not using OAC. Knowing that the efficacy of aspirin declines at aged > 70 years while the risk of bleeding increases, this observation was interesting. Studies have found that aged patients were less likely to receive antiplatelet therapy than younger patients.

A retrospective review of hospital admissions for ischemic stroke in patients with AF found that the percentage of patients receiving OAC treatment declined as age advanced, 75% of patients treated with OAC at aged <75 years and dropped to 33% when aged >85 years.

The efficacy of antiplatelet treatment crossed all aged patients with AF. Especially those with advanced age showed in a study after analyzing almost 9000 patients with AF, the benefit of stroke prevention by OAC was even more pronounced. Beyond considering advanced age as a contraindication to warfarin, fear of elderly patients to have more bleeding complications is a frequently cited reason why clinicians do not prescribe anticoagulant therapy to older patients. However, The Birmingham Atrial Fibrillation Treatment of the Aged trial demonstrated that there was no difference in major bleeding events comparing patients treated with warfarin and patients treated with aspirin while showing the superiority of warfarin over aspirin in reducing the risk of ischemic stroke in patients with AF aged >75 years.

In a recent review article done by Yates focused on NOACs for stroke prevention in older patients with AF had also concluded that NOACs are suitable alternatives to warfarin in preventing embolic events based on the benefits of these agents in this particular population. But, properties such as individual drug metabolism and route of elimination should be considered when older patients especially those with chronic kidney disease were given these agents. The reduction in stroke risk must be balanced against the increased risk of bleeding and currently there is no antidote existed to reverse the anticoagulant effect of NOACs.

Another significant factor associated with no OAC was stroke severity as measured by BI. This may be attributed to the consideration of the total dependency of daily activities, high risk of falling accidents, and tendency to bleed. Besides, previous clinical trials of stroke prevention in AF excluded patients with severe stroke, therefore effect and safety of OAC in this subgroup was not well understood. Considering our limited medical resources and the insurance reimbursement policy, these might partly explained why these patients were not giving OAC treatment.

Among the postulated reasons of not giving OAC, peptic ulcers or gastrointestinal tract bleeding comprised the majority followed by ischemic stroke with hemorrhagic transformation, anemia, history of old intracranial hemorrhage, gross hematuria, thrombocytopenia, and any ecchymosis. No significant difference was found but when comparing patients receiving only 1 antiplatelet agent and those with no antithrombotic therapy, patient with gastrointestinal bleeding and thrombocytopenia were likely to receive no treatment, in contrary, the percentage of unknown reason was only 5% in patients with no treatment compared to 44.6% in patients with antiplatelet agent. The results implied that doctors still considered antiplatelet agent was safer than OAC (either warfarin or NOACs) in this real-world clinical practice. Our observational data were similar to the recent report from England, 41% of the patients without reasons for not using warfarin when eligible.

There were limitations in our study. First, the results were from small numbers of subjects in a single hospital and medical center, and it may not apply to whole AF population in Taiwan. Second, we only discussed about anticoagulation therapy of secondary prevention for stroke, but not disclose the clinical practice of primary prevention in AF patients with a moderate to high risk of stroke. Third, some important issues such as the impact on clinical outcome or dropout rate between the users of warfarin and NOACs were not explored in the study, which warrants further follow-up.

CONCLUSIONS

NOACs improved the use of antithrombotic therapy in NVAF ischemic stroke patients for further embolic events prevention but age and stroke severity hindered the use of OAC. Although the percentage of patients with effective
anticoagulation treatment increased, it is apparently more room for improvement. Most of the patients still received antiplatelet agent for further stroke prevention.

REFERENCES

1. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. Arch Intern Med. 1987;147:1561–1564.

2. Marini C, De Santis F, Sacco S, et al. Contribution of atrial fibrillation to incidence and outcome of ischemic stroke: results from a population-based study. Stroke. 2005;36:1115–1119.

3. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. Circulation. 2014;130:e199–e267.

4. Jones C, Pollit V, Fitzmaurice D, Cowan C. The management of atrial fibrillation: summary of updated NICE guidance. BMJ. 2014;348: : 2014–65

5. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J. 2012;33:2719–2747.

6. Ogilvie IM, Newton N, Welner SA, et al. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med. 2010;123:638–645.e4.

7. Ogawa S, Aonuma K, Huang D, et al. Fact-finding survey of antithrombotic treatment for prevention of cerebral and systemic thromboembolism in patients with non-valvular atrial fibrillation in 9 countries of the Asia-Pacific region. J Arrhythmia. 2012;28:41–55.

8. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955–962.

9. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35–41.

10. Hsieh FI, Lien LM, Chen ST, et al. Get With the Guidelines-Stroke Registry: Get With the Guidelines-Stroke in Taiwan. Circulation. 2010;122:1116–1123.

11. Guo GB, Chang HW, Chen MC, et al. Underutilization of anticoagulation therapy in chronic atrial fibrillation. Jpn Heart J. 2001;42:55–65.

12. Lin LJ, Cheng MH, Lee CH, et al. Compliance with antithrombotic prescribing guidelines for patients with atrial fibrillation – a nationwide descriptive study in Taiwan. Clin Ther. 2008;30:1726–1736.

13. Yu HC, Tsai YF, Chen MC, Yeh CH. Underuse of antithrombotic therapy caused high incidence of ischemic stroke in patients with atrial fibrillation. Int J Stroke. 2012;7:112–117.

14. Dinh T, Nieuwlaat R, Tieleman RG, et al. Antithrombotic drug prescription in atrial fibrillation and its rationale among general practitioners, internists and cardiologists in The Netherlands – The EXAMINE-AF study. A questionnaire survey. Int J Clin Pract. 2007;61:24–31.

15. Walker AM, Bennett D. Epidemiology and outcomes in patients with atrial fibrillation in the United States. Heart Rhythm. 2008;5:1365–1372.

16. Zhao F, Loke C, Rankin SC, et al. Novel CYP2C9 genetic variants in Asian subjects and their influence on maintenance warfarin dose. Clin Pharmacol Ther. 2004;76:210–219.

17. Yuen E, Gueorguieva I, Wise S, et al. Ethnic differences in the population pharmacokinetics and pharmacodynamics of warfarin. J Pharmacokinet Pharmacodyn. 2010;37:3–24.

18. Lam MP, Cheung BM. The pharmacogenetics of the response to warfarin in Chinese. Br J Clin Pharmacol. 2012;73:340–347.

19. Fugh-Berman A. Herb-drug interactions. Lancet. 2000;355:134–138.

20. Shen AY, Chen W, Yao JF, et al. Effect of race/ethnicity on the efficacy of warfarin: potential implications for prevention of stroke in patients with atrial fibrillation. CNS Drugs. 2008;22:815–825.

21. Lip GY, Wang KL, Chiang CE. Non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in Asian patients with atrial fibrillation: time for a reappraisal. Int J Cardiol. 2014;180:e246–254.

22. Gao Q, Fu X, Wei JW, et al. Use of oral anticoagulation among stroke patients with atrial fibrillation in China: the ChinaQUEST (Quality evaluation of stroke care and treatment) registry study. Int J Stroke. 2013;8:150–154.

23. Apostolakis S, Sullivan RM, Olshansky B, et al. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAME-TT(2)R(2) score. Chest. 2013;144:1555–1563.

24. Van Spall HG, Wallentin L, Yusuf S, et al. Variation in warfarin dose adjustment practice is responsible for differences in the quality of anticoagulation control between countries and centers: an analysis of patients receiving warfarin in the randomized evaluation of long-term anticoagulation therapy (RE-LY) trial. Circulation. 2012;126:2309–2316.

25. Singer DE, Hellkamp AS, Piccini JP, et al. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF clinical trial. J Am Heart Assoc. 2013;2:e00067.

26. Goto S, Zhu J, Liu L, et al. Efficacy and safety of apixaban compared with warfarin for stroke prevention in patients with atrial fibrillation from East Asia: a subanalysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Trial. Am Heart J. 2014;168:303–309.

27. Bauer KA. Pros and cons of new oral anticoagulants. Hematology Am Soc Hematol Educ Programs. 2013;2013:464–470.

28. Kakkar AK, Mueller I, Bassand JP, et al. Risk profiles and antithrombotic treatment of patients newly diagnosed with atrial fibrillation at risk of stroke: perspectives from the international, observational, prospective GARFIELD registry. PLoS One. 2013;8:e03479.

29. Hylke EM, D’Antonio J, Evans-Molina C, et al. Translating the results of randomized trials into clinical practice: the challenge of warfarin candidacy among hospitalized elderly patients with atrial fibrillation. Stroke. 2006;37:1075–1080.

30. Partington SL, Abid S, Teo K, et al. Pre-admission warfarin use in patients with acute ischemic stroke and atrial fibrillation: The appropriate use and barriers to oral anticoagulant therapy: Thromb Res. 2007;120:663–669.

31. van Walraven C, Hart RG, Connolly S, et al. Effect of age on stroke prevention therapy in patients with atrial fibrillation: the atrial fibrillation investigators. Stroke. 2009;40:1410–1416.

32. Scowcroft AC, Lee S, Mant J. Thromboprophylaxis of elderly patients with AF in the UK: an analysis using the General Practice Research Database (GPRD) 2000–2009. Heart. 2013;99:127–132.

33. Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. Lancet. 2007;370:493–503.

34. Yates SW. Novel oral anticoagulants for stroke prevention in atrial fibrillation: a focus on the older patient. Int J Gen Med. 2013;6:167–180.

35. Rosenman MB, Baker L, Jing Y, et al. Why is warfarin underused for stroke prevention in atrial fibrillation? A detailed review of electronic medical records. Curr Med Res Opin. 2012;28:1407–1414.