Non–Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Asian Patients With Nonvalvular Atrial Fibrillation
Meta-Analysis

Kang-Ling Wang, MD; Gregory Y.H. Lip, MD; Shing-Jong Lin, MD, PhD; Chern-En Chiang, MD, PhD

Background and Purpose—The use of vitamin K antagonists (VKAs), the cornerstone treatment for stroke prevention in patients with atrial fibrillation, is limited by the perceived risk of serious bleeding in Asia. Non-VKA oral anticoagulants (NOACs) are safer alternatives. Here, we evaluate performance differences of NOACs between Asians and non-Asians.

Methods—We compared efficacy and safety of NOACs between patients enrolled in Asian and non-Asian countries using aggregate data from phase III clinical trials. The odds ratios (ORs [95% confidence interval]) were calculated by a random effects model.

Results—Comparing with VKAs, standard-dose NOACs reduced stroke or systemic embolism (OR=0.65 [0.52–0.83] versus 0.85 [0.77–0.93], P interaction=0.045) more in Asians than in non-Asians and were safer in Asians than in non-Asians about major bleeding (OR=0.57 [0.44–0.74] versus 0.89 [0.76–1.04], P interaction=0.004), hemorrhagic stroke (OR=0.32 [0.19–0.52] versus 0.56 [0.44–0.70], P interaction=0.046) in particular, whereas gastrointestinal bleeding was significantly increased in non-Asians (OR=0.79 [0.48–1.32] versus 1.44 [1.12–1.85], P interaction=0.041). Generally, low-dose NOACs were safer than VKAs without heterogeneity in efficacy and safety between Asians and non-Asians, except for ischemic stroke, major, and gastrointestinal bleeding.

Conclusions—Our findings suggest that standard-dose NOACs were more effective and safer in Asians than in non-Asians, whereas low-dose NOACs performed similarly in both populations. (Stroke. 2015;46:2555-2561. DOI: 10.1161/STROKEAHA.115.009947.)

Key Words: anticoagulants ▪ atrial fibrillation ▪ hemorrhage ▪ stroke

Stroke prevention with vitamin K antagonists (VKAs) is essential in the management of atrial fibrillation (AF). However, it has been generally perceived that Asian patients are naturally more sensitive to VKAs and have unacceptable higher rates of intracranial hemorrhage (ICH) even when international normalized ratio is ideally maintained. Consequently, VKAs have been largely underused or underdosed in Asian patients. Despite the average time in therapeutic range with VKAs was lower in Asian patients than that in non-Asian patients in clinical trials, the rates of major bleeding (ICH in particular) were significantly higher in Asian patients.

The development of non-VKA oral anticoagulants (NOACs) has changed the landscape of stroke prevention in patients with AF, with 4 agents available namely dabigatran, rivaroxaban, apixaban, and edoxaban being tested in large phase III clinical trials. The availability of NOACs is of paramount importance to Asian patients who are prone to bleeding, including devastating ICH with or without VKAs. The observations from the Japanese Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (J-ROCKET AF) might even imply that different dosing strategies should be applied according to ethnicities, weight, and renal function. Several prior observations suggest that NOACs were more preferentially indicated for stroke prevention in Asian patients with AF than VKAs.

Although each trial was powered to address primary efficacy and safety outcomes of the overall patients who have been enrolled, the benefit and risk profiles of NOACs in Asian patients need proper description given the fact that the
burden of AF and its associated complications is substantially higher in Asia than in the rest of the world because Asia is the most populated region and has fast-growing aging societies. Since nonwhite ethnics, particularly Asians, are a major factor attributable to ICH in anticoagulated patients, more Asian patients would have been deemed ineligible for treatment because of higher risk of bleeding. However, prior analyses of the individual approved NOACs were underpowered to show quantitative differences in various outcomes between Asian and non-Asian patients. In this meta-analysis, we aimed to assess the differences in efficacy and safety outcomes of NOACs in Asian patients compared with non-Asian patients that have not been addressed in previously published meta-analyses. Thus, these data are new and important for patients, physicians, and other healthcare professionals in this region.

Methods

Data Sources and Searches
We searched PubMed database (from January 2009 to July 2014), clinical trial registries, and relevant conference proceedings using the terms AF, warfarin, apixaban, dabigatran, edoxaban, rivaroxaban, and stroke. Ximelagatran was excluded from the search because it has been withdrawn from the market. No language restriction was imposed. The reference lists of published meta-analyses were also reviewed.

We considered randomized controlled trials comparing NOACs with VKAs in patients with nonvalvular AF. Trials were eligible for inclusion if they (1) involved >500 patients with nonvalvular AF; (2) reported both long-term efficacy and safety outcomes in Asian patients; and (3) had follow-up ≥1 year.

Data Extraction
All efficacy and safety outcomes were extracted. The efficacy outcomes include the composite of stroke or systemic embolism, ischemic stroke, myocardial infarction, and death from any cause; the safety outcomes were major bleeding, ICH, hemorrhagic stroke, and gastrointestinal bleeding. Definitions of those outcomes were the same across all trials, with the exception for major bleeding where the trial-specific definitions were adopted. In addition, gastrointestinal bleeding has not been universally reported in Asian patients. Data were used from the intention-to-treat populations for evaluating the efficacy outcomes except for J-ROCKET AF, which was primarily designed for evaluating safety outcomes. The differences in efficacy and safety outcomes of NOACs compared with VKAs among Asian and non-Asian patients were the interest of this meta-analysis.

Definition of Asian Patients
Because the individual patient-level data were not available, we could not ascertain the ethnicity of each patient enrolled in the trials. We therefore assumed that residence reported in the trials is a surrogate for ethnicity.

Data Synthesis and Analysis

Primary Analysis
Two doses of dabigatran and edoxaban were tested in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) and the Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48), respectively, and the low dose of rivaroxaban was compared with VKAs in J-ROCKET AF. Instead of combining data from different doses into one meta-analysis, which merges the therapeutic implications of different doses that might have diverse risk-benefit profiles, we conducted 2 separate meta-analyses. The meta-analysis for standard-dose NOACs included data of dabigatran 150 mg, edoxaban 60 mg, rivaroxaban 20 mg, and apixaban 5 mg. The meta-analysis for low-dose NOACs included data of dabigatran 110 mg, edoxaban 30 mg, and rivaroxaban 15 mg.

Sensitivity Analysis
Data of Asian patients have not been homogenously published in detail. In the prior subanalyses reporting efficacy/safety among Asian and non-Asian patients, there were 5, 1, and 3 Asian countries included as non-Asian countries in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE), and ENGAGE AF-TIMI 48, respectively. In addition, patients enrolled in Asian countries might not necessarily be ethnically Asian, vice versa. To mitigate the confounding of such heterogeneous data, we performed 3 sensitivity analyses by (1) examining data of 3 factor Xa inhibitors, and using (2) ethnicity-level, and (3) region-level information available from regulatory agencies. The outcome data used for sensitivity analyses were limited. Therefore, we could only investigate the composite of stroke or systemic embolism and major bleeding with respect to standard-dose NOACs compared with VKAs.

The odds ratio (OR) and associated 95% confidence interval (CI) were calculated for each outcome and trial separately and for the pooled results that were compared with DerSimonian and Laird random effects model. Heterogeneity between trials was assessed using the Cochran Q statistic and I² test. Interaction between Asian and non-Asian patients about therapeutic outcomes of NOACs compared with VKAs was systematically tested. Statistical analysis was performed using Comprehensive Meta-Analysis software, version 2 (Biostat Inc, NJ).

Results
Of the 78 studies identified from the literature search, 73 were excluded because of reports of the trial design, subgroup analyses without data of Asian patients, short follow-up, and limited patient numbers (Figure I in the online-only Data Supplement). The characteristics of the trials and treatment included in this meta-analysis are shown in Table I in the online-only Data Supplement. The 5 included studies namely RE-LY, ROCKET AF, J-ROCKET AF, ARISTOTLE, and ENGAGE AF-TIMI 48 comprised 8928 Asian patients (5250 with NOACs and 3678 with VKAs) and 64,033 non-Asian patients (37,800 with NOACs and 26,233 with VKAs).

Standard-Dose NOACs Versus VKAs
The comparative efficacy of standard-dose NOACs and VKAs is presented in Figure 1. Standard-dose NOACs significantly reduced the composite of stroke or systemic embolism both in Asian and non-Asian patients (OR, 0.65; 95% CI, 0.52–0.83; P<0.001 for Asian patients; OR, 0.85; 95% CI, 0.77–0.93; P<0.001 for non-Asian patients). The reduction was more prominent in Asian patients than in non-Asian patients (P=interaction=0.045). The effect of standard-dose NOACs on ischemic stroke and myocardial infarction was comparable with VKAs in both Asian and non-Asian patients (P=interaction=0.673 and 0.977, respectively). All-cause mortality was significantly lower in both with standard-dose NOACs than with VKAs (OR, 0.80; 95% CI, 0.65–0.98; P=0.030 for Asian patients; OR, 0.91; 95% CI, 0.86–0.97; P=0.003 for non-Asian patients; P=interaction=0.219).

Figure 2 shows the preferential benefit of standard-dose NOACs in safety outcomes in Asian patients. Standard-dose patients. Standard-dose...
NOACs reduced major bleeding more in Asian than in non-Asian patients (OR, 0.57; 95% CI, 0.44–0.74; P<0.001 for Asian patients; OR, 0.89; 95% CI, 0.76–1.04; P=0.143 for non-Asian patients; P interaction=0.004). ICH was significantly reduced in both with standard-dose NOACs (OR, 0.33; 95% CI, 0.22–0.50; P<0.001 for Asian patients; OR, 0.52; 95% CI, 0.42–0.64; P<0.001 for non-Asian patients; P interaction=0.059). Standard-dose NOACs had a substantial reduction in hemorrhagic stroke, which was more notable in Asian than in non-Asian patients (OR, 0.32; 95% CI, 0.19–0.52; P<0.001 for Asian patients; OR, 0.56; 95% CI, 0.44–0.70; P<0.001 for non-Asian patients; P interaction=0.046) compared with VKAs. Moreover, standard-dose NOACs increased the risk of gastrointestinal bleeding in non-Asian patients but not in Asian patients (OR, 1.44; 95% CI, 1.12–1.85; P=0.005 for non-Asian patients; OR, 0.79; 95% CI, 0.48–1.32; P=0.378 for Asian patients; P interaction=0.041).

Low-Dose NOACs Versus VKAs
The comparative efficacy of low-dose NOACs and VKAs with regard to the various efficacy outcomes is presented in Figure 3. Low-dose NOACs had similar efficacy to VKAs on stroke or systemic embolism and ischemic stroke both in Asian and non-Asian patients (P interaction=0.353 and 0.504, respectively). With regard to myocardial infarction, non-Asian patients had more events with low-dose NOACs than with VKAs (OR, 1.28; 95% CI, 1.06–1.55; P=0.010), whereas the effect of low-dose NOACs seemed to be similar to VKAs in Asian patients (OR, 0.92; 95% CI, 0.48–1.79; P=0.816); however, there was no statistic heterogeneity (P interaction=0.352). Low-dose NOACs were associated with a significant reduction in all-cause mortality in non-Asian patients and a trend for a reduction in Asian patients (P interaction=0.934).

The safety outcomes of low-dose NOACs are presented in Figure 4. Low-dose NOACs reduced major bleeding, ICH, and hemorrhagic stroke in both Asian and non-Asian patients (P interaction=0.579, 0.661, and 0.944, respectively). There was no difference in gastrointestinal bleeding in Asians and non-Asians (P interaction=0.460).

Sensitivity Analysis
The sensitivity analysis undertaken using factor Xa inhibitor trials showed parallel results to the primary analyses except for stroke or systemic embolism (Table II in the online-only Data
Supplement). Additional analyses using data available from the regulatory agency indicated the qualitatively similar results to our primary analyses that standard-dose NOACs significantly reduced stroke or systemic embolism and major bleeding to a greater degree in Asian than in non-Asian patients (Figures II and III in the online-only Data Supplement).

**Discussion**

Our study is the first meta-analysis of large phase III clinical trials that compared NOACs with VKAs in Asian and non-Asian patients with regard to both efficacy and safety outcomes. This analysis included >8000 Asian patients; the responses to NOACs were qualitatively similar between Asian and non-Asian patients with quantitatively greater benefits in Asian patients. Our data suggest that both standard-dose and low-dose NOACs are preferentially indicated in Asian patients for the prevention of AF-associated stroke rather than VKAs.

Previous meta-analyses consistently showed that standard-dose NOACs were more effective than VKAs on the reduction of stroke or systemic embolism. In our analysis, standard-dose NOACs were more effective than VKAs in both Asian and non-Asian patients, but NOACs fared even better in Asian patients. In addition, standard-dose NOACs were more effective on the reduction of hemorrhagic stroke in Asian than in non-Asian patients, which is most likely attributed to a higher bleeding risk with VKAs in Asian patients.

The major criticism of standard-dose NOACs, which has been consistently shown in previous meta-analyses, was that they were less effective on the reduction of major bleeding. In our analysis, however, standard-dose NOACs were still effective in Asian patients, compared with VKAs. In non-Asian patients, the beneficial effect on major bleeding was marginal. It is possible that NOACs are more effective in Asian patients than in non-Asian patients because the risk of major bleeding in Asian with VKAs is generally higher than in non-Asian patients even though more Asian patients had international normalized ratio <2.0 and less Asian patients had international normalized ratio >3.0. The absolute risk of major bleeding with NOACs was numerically lower in Asian than in non-Asian patients (the annual risk was 2.17% versus 3.52%, 3.44% versus 3.60%, and 2.02% versus 2.15%, with dabigatran 150 mg, rivaroxaban 20 mg, and apixaban 5 mg, respectively). Therefore, the absolute risk reduction in major bleeding by standard-dose NOACs was generally greater in Asian than in non-Asian patients.

![Figure 2](http://stroke.ahajournals.org/content/17/5/2558/F2.large.jpg)

**Figure 2.** Safety outcomes of major bleeding (A), intracranial hemorrhage (B), hemorrhagic stroke (C), and gastrointestinal bleeding (D) for the standard-dose non–vitamin K antagonist (VKA) oral anticoagulants (NOACs) vs VKAs. CI indicates confidence interval; and OR, odds ratio.
Another important criticism of standard-dose NOACs is an increase in risk of gastrointestinal bleeding.25–28 We found that the increased risk of gastrointestinal bleeding was only significant in non-Asian patients. Indeed, the numbers for gastrointestinal bleeding in Asian patients were not reported either in ROCKET AF or in ARISTOTLE, but the risk of gastrointestinal bleeding was numerically higher in overall patients with rivaroxaban than with VKAs (3.15% versus 2.16%) in ROCKET AF.8 The risk of digestive tract bleeding was numerically similar in overall patients with apixaban versus VKAs (0.78% versus 0.88%).29 Unlike other bleeding events, gastrointestinal bleeding with VKAs was similar in Asian and in non-Asian patients (1.41% versus 1.01% and 1.11% versus 1.24% for Asian patients versus non-Asian patients in RE-LY and ENGAGE AF-TIMI 48, respectively). Concomitant antiplatelet therapy is an independent predictor for gastrointestinal bleeding.28,30,31 In RE-LY, the concomitant use of aspirin was more common and the use of proton pump inhibitors was less common in Asian than in non-Asian patients, but gastrointestinal bleeding was not increased by dabigatran 150 mg.20 Our findings may suggest that standard-dose NOACs should not be avoided in Asian patients simply on the basis of the risk of gastrointestinal bleeding.

Low-dose NOACs are similarly effective as VKAs in prevention against stroke or systemic embolism for both Asian and non-Asian patients but might not be as effective for protection against ischemic stroke. They are safer than VKAs with respect to hemorrhagic stroke, and no difference could be found between Asian and non-Asian patients. Our analysis suggests that low-dose NOACs were effective on the reduction of major bleeding and ICH in both Asian and non-Asian patients, compared with VKAs. Again, no signal of increased gastrointestinal bleeding was observed. Based on our analysis, low-dose NOACs can be effective and safe alternatives to VKAs in Asian patients and should be considered in patients with higher bleeding risk.

Finally, the general mechanisms involved with the differential effects of NOACs compared with VKAs between Asian and non-Asian patients are yet to be determined. Genetically, Asian patients are more likely to be VKA sensitive or highly sensitive responders, who seem prone to excessive bleeding.32 Except for the variations in distributions of genetic polymorphisms for VKA metabolism,33,34 Asian patients tended to have lower body weight, smaller proportions of prior myocardial infarction, VKA experiences, and the concomitant use of gastric antacid drugs.
and greater proportions of impair renal function, prior stroke, nonparoxysmal AF, and the use of antplatelet medications.20–23 Those demographic differences might be clinically relevant factors for anticoagulant treatment other than ethnic per se.

Limitations
Our analysis has several limitations. First, we did not have individual patient-level data from trials included for this meta-analysis. Without individual patient-level information, some of the patients enrolled in Asian countries described in our meta-analysis might not be ethnically Asian, and some of the Asian patients were included in non-Asian populations in the analyses of clinical trials.21–23 However, the majority of Asian patients would be enrolled in Asia as, for example, only 11 Asian patients were recruited at US sites in ARISTOTLE. In addition, the sensitivity analyses with the available information at ethnic and regional levels from the regulatory agency showed similar results to our primary analyses. Second, the benefit of NOACs in Asian population may be related to genetic polymorphism for VKA metabolism, and lower body weight and creatinine clearance. However, relative efficacy of NOACs is consistent across a broad range of vulnerable patients,27 and a greater reduction in bleeding risk with NOACs compared with VKAs was seen across genotypes,26 body weight,7–9 and renal function.27 Finally, there was some heterogeneity between included trials. Therefore, we used a random effects model to account for heterogeneity within individual trials.

Conclusions
Both standard-dose and low-dose NOACs performed equally well, or even better, with regard to efficacy and safety in Asian than in non-Asian patients. Standard-dose NOACs are preferred over VKAs in Asian patients, whereas low-dose NOACs are effective and safe alternatives to VKAs.

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Disclosures
Dr Wang has received honoraria from Bayer and Daiichi-Sankyo. Dr Lip has served as a consultant for Bayer, Biotronik, BMS/Pfizer,
Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Merck, Portola, and Sanofi and has been on the speaker bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Medtronic. Dr Chiang has been on the speaker bureau for Bayer, Boehringer Ingelheim, and Daiichi-Sankyo. Dr Lin reports no conflicts.

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Supplementary Material

Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Asian Patients with Non-valvular Atrial Fibrillation: A Meta-analysis

Running title: NOACs in Asians

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Supplementary table I. Baseline characteristics of 5 phase III clinical trials.

Supplementary table II. Pooled estimate of 3 standard-dose factor Xa inhibitors compared with vitamin K antagonists by DerSimonian and Laird random-effects model.

Supplementary figure I. PRISMA diagram.

Supplementary figure II. Sensitivity analyses of standard-dose NOACs according to ethnicities.

Supplementary figure III. Sensitivity analyses of standard-dose NOACs according to regions.
Supplementary table I. Baseline characteristics of 5 phase III clinical trials.

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<td></td>
</tr>
<tr>
<td>NOACs therapy</td>
<td>Dabigatran 110mg or 150mg twice daily</td>
<td>Rivaroxaban 20mg once daily (15mg for patients with CrCl of 30-49 mL/min)</td>
<td>Apixaban 5mg twice daily (2.5mg for patients with ≥2 of the following criteria: age ≥80 yrs, weight ≤60 kg, or a serum creatinine ≥1.5 mg/dl)</td>
<td>Edoxaban 30mg or 60mg once daily (15mg or 30mg, respectively for patients with CrCl of 30-50 mL/min, weight ≤60 kg, or the concomitant use of potent P-glycoprotein inhibitors)</td>
<td>Rivaroxaban 15 mg once daily (10 mg for patients with CrCl of 30-49 mL/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
INR targets for VKAs

<table>
<thead>
<tr>
<th></th>
<th>2.0-3.0 (2.0-2.6 for Japanese patients aged ≥70 yrs)</th>
<th>2.0-3.0</th>
<th>2.0-3.0</th>
<th>2.0-3.0</th>
<th>2.0-3.0 (1.6-2.6 for patients aged ≥70 yrs)</th>
</tr>
</thead>
</table>

*CrCl <50 mL/min
†warfarin
‡rivaroxaban
§standard dose edoxaban
||low dose edoxaban

CrCl = creatinine clearance; INR = international normalized ratio; MI = myocardial infarction; NOAC = non-vitamin K antagonist oral anticoagulant; TTR = time in therapeutic range; VKA = vitamin K antagonist
## Supplementary table II. Pooled estimate of 3 standard-dose factor Xa inhibitors compared with vitamin K antagonists by DerSimonian and Laird random-effects model.

<table>
<thead>
<tr>
<th></th>
<th>Asian patients</th>
<th></th>
<th>Non-Asian patients</th>
<th></th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P value</td>
<td>OR (95% CI)</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Stroke or SE</td>
<td>0.73 (0.56-0.95)</td>
<td>0.021</td>
<td>0.87 (0.78-0.97)</td>
<td>0.010</td>
<td>0.227</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.03 (0.75-1.42)</td>
<td>0.847</td>
<td>0.97 (0.86-1.09)</td>
<td>0.610</td>
<td>0.717</td>
</tr>
<tr>
<td>MI</td>
<td>1.00 (0.56-1.79)</td>
<td>0.996</td>
<td>0.91 (0.78-1.06)</td>
<td>0.216</td>
<td>0.753</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.80 (0.61-1.04)</td>
<td>0.094</td>
<td>0.91 (0.85-0.98)</td>
<td>0.007</td>
<td>0.329</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>0.57 (0.42-0.79)</td>
<td>0.001</td>
<td>0.86 (0.70-1.04)</td>
<td>0.126</td>
<td>0.037</td>
</tr>
<tr>
<td>ICH</td>
<td>0.31 (0.19-0.51)</td>
<td>&lt;0.001</td>
<td>0.55 (0.43-0.71)</td>
<td>&lt;0.001</td>
<td>0.041</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.34 (0.20-0.58)</td>
<td>&lt;0.001</td>
<td>0.60 (0.47-0.77)</td>
<td>&lt;0.001</td>
<td>0.060</td>
</tr>
</tbody>
</table>

CI = confidence interval; ICH = Intracranial hemorrhage; MI = myocardial infarction; OR = odds ratio; SE = systemic embolism
Supplementary figure I. PRISMA diagram.

77 records identified through PubMed database searching
1 additional record identified through abstract reviews

78 records after duplicates removed

78 records screened

70 records excluded
10 meta-analyses
4 rationale and design
4 main results of overall trials
52 secondary analyses without results of Asian patients

8 articles assessed for eligibility

3 articles excluded
1 short follow-up
2 limited patient numbers

5 studies included in qualitative synthesis

5 studies included in quantitative synthesis (meta-analysis)
Supplementary figure II. Sensitivity analyses of standard-dose NOACs in stroke or systemic embolism (A) and major bleeding (B) according to ethnicities.

*Event numbers for ENGAGE AF-TIMI 48 have been estimated from published confidence intervals.

### A. Stroke or systemic embolism

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY, 150mg</td>
<td>25/965</td>
<td>52/955</td>
<td>0.46 (0.28-0.75)</td>
<td>0.061</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>36/897</td>
<td>50/889</td>
<td>0.70 (0.45-1.09)</td>
<td>0.099</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>50/1310</td>
<td>77/1332</td>
<td>0.72 (0.49-1.04)</td>
<td>0.055</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>30/956</td>
<td>48/963</td>
<td>0.62 (0.39-0.98)</td>
<td>0.035</td>
</tr>
<tr>
<td>Overall Effect</td>
<td></td>
<td></td>
<td>0.63 (0.51-0.76)</td>
<td>0.001</td>
</tr>
<tr>
<td>Q= 2.3 (P= 0.521)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P= 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Asian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY, 150mg</td>
<td>109/5111</td>
<td>150/5067</td>
<td>0.71 (0.56-0.92)</td>
<td>0.012</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>233/6184</td>
<td>256/6201</td>
<td>0.91 (0.76-1.09)</td>
<td>0.018</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>162/7810</td>
<td>186/7748</td>
<td>0.65 (0.69-1.05)</td>
<td>0.070</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>152/6049</td>
<td>183/6032</td>
<td>0.83 (0.66-1.03)</td>
<td>0.184</td>
</tr>
<tr>
<td>Overall Effect</td>
<td></td>
<td></td>
<td>0.84 (0.75-0.93)</td>
<td>0.027</td>
</tr>
<tr>
<td>Q= 2.4 (P= 0.496)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P= 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Interaction P= 0.022

### B. Major bleeding

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY, 150mg</td>
<td>42/965</td>
<td>68/955</td>
<td>0.59 (0.40-0.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>44/894</td>
<td>70/887</td>
<td>0.69 (0.41-0.99)</td>
<td>0.047</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>45/1302</td>
<td>81/1328</td>
<td>0.55 (0.38-0.80)</td>
<td>0.001</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>69/956</td>
<td>88/963</td>
<td>0.77 (0.56-1.07)</td>
<td>0.080</td>
</tr>
<tr>
<td>Overall Effect</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q= 2.1 (P= 0.545)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P= 0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-Asian

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY, 150mg</td>
<td>357/5111</td>
<td>353/5067</td>
<td>1.00 (0.86-1.17)</td>
<td>0.880</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>351/6167</td>
<td>316/6105</td>
<td>1.12 (0.96-1.31)</td>
<td>0.130</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>262/7786</td>
<td>381/7724</td>
<td>0.72 (0.62-0.85)</td>
<td>0.000</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>357/6040</td>
<td>444/6032</td>
<td>0.79 (0.68-0.91)</td>
<td>0.002</td>
</tr>
<tr>
<td>Overall Effect</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Q= 20.0 (P&lt;0.001)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>P= 88.0%</td>
<td></td>
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</tr>
</tbody>
</table>

Interaction P= 0.025
Supplementary figure III. Sensitivity analyses of standard-dose NOACs in stroke or systemic embolism (A) and major bleeding (B) according to regions.

*included China, Hong Kong, India, Japan Malaysia, Philippines, Singapore, South Korea, Taiwan, and Thailand
†included Australia, China, Hong Kong, India, Malaysia, New Zealand, Philippines, Singapore, South Korea, Taiwan, and Thailand
‡included Australia, China, Hong Kong, India, Japan, Malaysia, Philippines, Singapore, South Korea, and Taiwan
§included Australia, China, India, Japan, New Zealand, Philippines, South Africa, South Korea, Taiwan, and Thailand

<table>
<thead>
<tr>
<th>Region</th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
<th>Region</th>
<th>NOAC Event/Total</th>
<th>VKA Event/Total</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia Pacific</td>
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<td></td>
<td></td>
<td>Asia Pacific</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY, 150mg*</td>
<td>25/933</td>
<td>53/926</td>
<td>0.45 (0.28-0.74)</td>
<td>RE-LY, 150mg*</td>
<td>39/933</td>
<td>66/926</td>
<td>0.57 (0.38-0.85)</td>
</tr>
<tr>
<td>ROCKET AF†</td>
<td>45/1055</td>
<td>54/1054</td>
<td>0.83 (0.55-1.24)</td>
<td>ROCKET AF†</td>
<td>63/1052</td>
<td>81/1052</td>
<td>0.76 (0.54-1.07)</td>
</tr>
<tr>
<td>ARISTOTLE‡</td>
<td>52/1456</td>
<td>80/1460</td>
<td>0.64 (0.45-0.91)</td>
<td>ARISTOTLE‡</td>
<td>51/1446</td>
<td>96/1456</td>
<td>0.52 (0.37-0.73)</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg§</td>
<td>35/1120</td>
<td>55/1123</td>
<td>0.63 (0.41-0.96)</td>
<td>ENGAGE AF, 60mg§</td>
<td>85/1120</td>
<td>99/1123</td>
<td>0.65 (0.63-1.15)</td>
</tr>
<tr>
<td>Overall Effect</td>
<td></td>
<td></td>
<td>0.64 (0.52-0.78)</td>
<td>Overall Effect</td>
<td></td>
<td></td>
<td>0.67 (0.53-0.86)</td>
</tr>
<tr>
<td>Q= 3.5 (P= 0.326)</td>
<td></td>
<td></td>
<td></td>
<td>Q= 5.6 (P= 0.130)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>F= 13.3%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Rest of the world</td>
<td></td>
<td></td>
<td></td>
<td>Rest of the world</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RE-LY, 150mg</td>
<td>109/5143</td>
<td>140/5098</td>
<td>0.72 (0.59-0.92)</td>
<td>RE-LY, 150mg</td>
<td>360/5143</td>
<td>355/5096</td>
<td>1.01 (0.86-1.17)</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>224/6026</td>
<td>252/6036</td>
<td>0.89 (0.74-1.06)</td>
<td>ROCKET AF</td>
<td>332/6009</td>
<td>305/6030</td>
<td>1.10 (0.94-1.29)</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>160/7664</td>
<td>185/7621</td>
<td>0.86 (0.69-1.06)</td>
<td>ARISTOTLE</td>
<td>276/7640</td>
<td>366/7656</td>
<td>0.74 (0.63-0.87)</td>
</tr>
<tr>
<td>ENGAGE AF, 60mg</td>
<td>147/5892</td>
<td>177/5889</td>
<td>0.83 (0.66-1.03)</td>
<td>ENGAGE AF, 60mg</td>
<td>333/5892</td>
<td>425/5889</td>
<td>0.77 (0.66-0.89)</td>
</tr>
<tr>
<td>Overall Effect</td>
<td></td>
<td></td>
<td>0.83 (0.75-0.93)</td>
<td>Overall Effect</td>
<td></td>
<td></td>
<td>0.89 (0.74-1.07)</td>
</tr>
<tr>
<td>Q= 1.8 (P= 0.608)</td>
<td></td>
<td></td>
<td></td>
<td>Q= 17.9 (P&lt;0.001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F= 0.0%</td>
<td></td>
<td></td>
<td></td>
<td>F= 83.2%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction P= 0.625</td>
<td></td>
<td></td>
<td></td>
<td>Interaction P= 0.072</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Reference


Non–Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Asian Patients With Nonvalvular Atrial Fibrillation

Meta-Analysis

Kang-Ling Wang, MD 1,2,3,4; Gregory Y.H. Lip, MD 5,6; Shing-Jong Lin, MD, PhD 2,3,4; Chern-En Chiang, MD 1,2,3,4; Aalborg University, Aalborg, Denmark

1 General Clinical Research Center; 2 Department of Medical Research; 3 Division of Cardiology, Taipei Veterans General Hospital, Taipei, Taiwan; 4 School of Medicine, National Yang-Ming University, Taipei, Taiwan; 5 University of Birmingham, Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom; and 6 Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Non–Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Asian Patients

Background and Objectives: Vitamin K antagonist (VKA) is a long-acting oral anticoagulant which is effective for preventing stroke in atrial fibrillation when compared to placebo. However, VKA is expensive and inconvenient. Non–Vitamin K antagonist oral anticoagulants (NOACs) are relatively new oral anticoagulants which are effective for stroke prevention in atrial fibrillation. This meta-analysis aimed to evaluate the noninferiority of NOACs compared to VKA for stroke prevention in Asian patients.

Methods: The Cochrane Library and PubMed were searched for randomized controlled trials comparing NOACs and VKA for stroke prevention in nonvalvular atrial fibrillation. The primary outcome was the incidence of stroke or system embolic events. The secondary outcomes were major hemorrhage, minor hemorrhage, and all-cause mortality. The risk of bias was assessed using the Cochrane Collaboration’s tool.

Results: Five randomized controlled trials comparing NOACs and VKA for stroke prevention in Asian patients were included in the meta-analysis. The incidence of stroke or systemic embolic events was not significantly different between NOACs and VKA (OR = 0.86, 95% CI: 0.66-1.13, P = 0.26). Major hemorrhage was not significantly different between NOACs and VKA (OR = 0.71, 95% CI: 0.44-1.17, P = 0.19). Minor hemorrhage was not significantly different between NOACs and VKA (OR = 1.15, 95% CI: 0.90-1.47, P = 0.27). All-cause mortality was not significantly different between NOACs and VKA (OR = 1.11, 95% CI: 0.72-1.71, P = 0.65).

Conclusion: NOACs are noninferior to VKA in the prevention of stroke or systemic embolic events in Asian patients with nonvalvular atrial fibrillation. NOACs may be a reasonable alternative to VKA for stroke prevention in Asian patients.
データの合成および解析

主要解析

Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) および Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) では、ダビガトランおよびエドキサバンを2用量で検討する試験であった。J-ROCKET AFでは、リバロキサバンの低用量投与とVKAが比較された。異なる用量のデータを1つのメタアナリシスに統合すると、用量により異なったリスク-利益特性を持つ治療の影響が融合してしまうため、代わりに2つのメタアナリシスを別々に実施した。標準用量のNOACのメタアナリシスには、ダビガトラン150mg、エドキサバン60mg、リバロキサバン20mg、アピガキサバン5mgのデータを入れた。低用量のNOACのメタアナリシスには、ダビガトラン110mg、エドキサバン30mg、リバロキサバン15mgのデータを入れた。

感度分析

アジア系患者のデータは、均一的に詳しく発表されていなかった。アジア系患者および非アジア系患者での有効性/安全性を報告した過去のサブ解析では、アジア諸国が非アジア諸国に含まれており、Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation（ROCKET AF）では5ヵ国、Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation（ARISTOTLE）では1ヵ国、ENGAGE AF-TIMI 48では3ヵ国が非アジア諸国に該当していた。また、アジア諸国で参加した患者は必ずしも純粋なアジア系とは限らず、逆にもあった。このような異質なデータの交絡を軽減するため、（1）3つの第Xa因子抑制薬のデータを調査することにより、さらに監督省庁から入手した（2）区域レベルの情報および（3）地域レベルの情報を使用することにより、3回の感度分析を実施した。感度分析に用いるデータ数の有効性は限られており、したがって、標準用量のNOACとVKAによる脳卒中/全身性塞栓症の複合項目と大出血の比較しかできなかった。

アジア系患者の定義

個人患者レベルのデータは得られなかったため、これらに参加した各患者の民族性は確認できなかった。したがって試験で報告された居住地を民族性の代わりとした。

データの合成および解析

主要解析

Randomized Evaluation of Long-Term Anticoagulation Therapy（RE-LY）およびEffective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48（ENGAGE AF-TIMI 48）では、ダビガトランおよびエドキサバンを2用量で検討する試験であった。J-ROCKET AFでは、リバロキサバンの低用量投与とVKAが比較された。異なる用量のデータを1つのメタアナリシスに統合すると、用量により異なったリスク-利益特性を持つ治療の影響が融合してしまうため、代わりに2つのメタアナリシスを別々に実施した。標準用量のNOACのメタアナリシスには、ダビガトラン150mg、エドキサバン60mg、リバロキサバン20mg、アピガキサバン5mgのデータを入れた。低用量のNOACのメタアナリシスには、ダビガトラン110mg、エドキサバン30mg、リバロキサバン15mgのデータを入れた。

感度分析

アジア系患者のデータは、均一的に詳しく発表されていなかった。アジア系患者および非アジア系患者での有効性/安全性を報告した過去のサブ解析では、アジア諸国が非アジア諸国に含まれており、Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation（ROCKET AF）では5ヵ国、Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation（ARISTOTLE）では1ヵ国、ENGAGE AF-TIMI 48では3ヵ国が非アジア諸国に該当していた。また、アジア諸国で参加した患者は必ずしも純粋なアジア系とは限らず、逆にもあった。このような異質なデータの交絡を軽減するため、（1）3つの第Xa因子抑制薬のデータを調査することにより、さらに監督省庁から入手した（2）区域レベルの情報および（3）地域レベルの情報を使用することにより、3回の感度分析を実施した。感度分析に用いるデータ数の有効性は限られており、したがって、標準用量のNOACとVKAによる脳卒中/全身性塞栓症の複合項目と大出血の比較しかできなかった。

アジア系患者の定義

個人患者レベルのデータは得られなかったため、これらの試験に参加した各患者の民族性は確認できなかった。したがって試験で報告された居住地を民族性の代わりとした。

データの合成および解析

主要解析

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検査の異質性は Cochran Q 統計量および F 検定で評価した。VKA と NOAC で比較した治療効果に関するアジア系患者と非アジア系患者の交互作用を体系的に検討した。統計解析は Comprehensive Meta-Analysis ソフトウェアのバージョン 2（Biostat Inc, NJ）で実施した。

結 果

文献検索から特定した 78 破見のうち 73 破見は、破見デザイン、アジア系患者のデータがないサブグループ解析、短期追跡調査の報告および患者数が少ない報告であったため除外した（オンラインデータ補遺図 1）。本メタアナリシスでは対象とした研究および治療の特徴をオンラインデータ補遺表 1 に示す。対象とした 55 の試験、すなわち RE-LY, ROCKET AF, J-ROCKET AF, ARISTOTLE, ENGAGE AF-TIMI 48 は、アジア系患者 8,928 例（NOAC 5,250 例および VKA 3,678 例）および非アジア系患者 64,033 例（NOAC 37,800 例および VKA 26,233 例）で構成されていた。

標準用量の NOAC と VKA

標準用量の NOAC はアジア系患者および非アジア系患者の脳卒中／全身性塞栓症の複合項目に有意に減少させた（アジア系患者：OR = 0.65, 95% CI: 0.52 ~ 0.83, P < 0.001。非アジア系患者：OR = 0.85, 95% CI: 0.77 ~ 0.93, P < 0.001）。上記の減少は非アジア系患者よりアジア系患者で顕著であった（P interaction = 0.045）。虚血性脳卒中および心筋梗塞に対する標準用量の NOAC の影響は、アジア系患者および非アジア系患者で VKA と同等であった（P interaction = 0.673 および 0.977）。標準用量の NOAC では、VKA に比べ両患者群の全死因死亡が有意に低下した（アジア系患者：OR = 0.80, 95% CI: 0.65 ~ 0.98, P = 0.030。非アジア系患者：OR = 0.91, 95% CI: 0.86 ~ 0.97, P = 0.003。P interaction = 0.219）。

アジア系患者の安全性評価項目については、標準用量の NOAC がより有益であることが図 2 に示される。標準用量の NOAC は非アジア系患者よりアジア系患者の大出出血を減少させた（アジア系患者：OR = 0.57, 95% CI: 0.44 ~ 0.74, P < 0.001。非アジア系患者：OR = 0.89, 95% CI: 0.76 ~ 1.04, P = 0.143。P interaction = 0.004）。ICH は標準用量の NOAC により両患者群で有意に減少した（アジア系患者：OR = 0.33, 95% CI: 0.22 ~ 0.50, P < 0.001。非アジア系患者：OR = 0.52, 95% CI: 0.42 ~ 0.64, P < 0.001。P interaction = 0.059）。また、標準用量 NOAC は VKA に比べ出血性脳卒中を大幅に減少させ、これは非アジア系患者よりアジア系患者に顕著であった（アジア系患者：OR = 0.32, 95% CI: 0.19 ~ 0.52, P < 0.001。非アジア系患者：OR = 0.56, 95% CI: 0.44 ~ 0.70, P < 0.001。P interaction = 0.046）。さらに、標準用量の NOAC により非アジア系患者の消化管出血リスクは増加したが、アジア系患者のリスクは増加しなかった（非アジア系患者：OR = 1.44, 95% CI: 1.12 ~ 1.85, P = 0.005。アジア系患者：OR = 0.79, 95% CI: 0.48 ~ 1.32, P = 0.378。P interaction = 0.041）。

低用量の NOAC と VKA

さまざまな有効性評価項目に関して、低用量の NOAC と VKA の有効性の比較を図 3 に示す。脳卒中／全身性塞栓症と虚血性脳卒中に対する低用量の NOAC の有効性は、アジア系患者および非アジア系患者のいずれにおいても VKA と同程度であった（それぞれ P interaction = 0.353 および 0.504）。心筋梗塞に関しては、低用量の NOAC を投与した非アジア系患者に VKA もより多くのイベントが認められた（OR = 1.28, 95% CI: 1.06 ~ 1.55, P = 0.010）。アジア系患者では低用量の NOAC と VKA の効果は同程度のようであった（OR = 0.92, 95% CI: 0.48 ~ 1.79, P = 0.816）。しかし統計学的異質性は認められなかった（P interaction = 0.352）。低用量の NOAC は非アジア系患者における全死因による死亡の有意な低下をもたらし、アジア系患者では低下傾向がみられた（P interaction = 0.934）。

低用量の NOAC の安全性評価項目を図 4 に示す。低用量の NOAC はアジア系患者および非アジア系患者の大出血、ICH、出血性脳卒中を減少させた（それぞれ 0.661, 0.944。P interaction = 0.579）。アジア系患者および非アジア系患者の消化管出血に差は認められなかった（P interaction = 0.460）。

感度分析

第 Xa 因子阻害薬の試験を使用して実施した感度分析は、脳卒中／全身性塞栓症を除き、主要解析に沿った結果を示した（オンラインデータ補遺図 II）。監督委員会から入手したデータの追加分析の結果も本主要解析と質的にほぼ同じ結果となり、標準用量の NOAC は非アジア系患者に比べアジア系患者の脳卒中／全身性塞栓症および大出血を有意に減少させた（オンラインデータ補遺図 II および III）。

考察

本研究では、アジア系患者および非アジア系患者で
NOAC と VKA の有効性および安全性を比較した大規模な第 III 相臨床試験のメタアナリシスとして、最初の研究であった。8,000 例を超えるアジア系患者が解析の対象となった。アジア系患者および非アジア系患者の NOAC に対する有効性は質的に似ていたが、量的な利益はアジア系患者の方が大きかった。本研究データから、アジア系患者の AF に関連脳卒中を予防する場合、標准用量および低用量の NOAC いずれも VKA より優先的に投与すべきであることが示唆される。

過去のメタアナリシスで標準用量の NOAC は VKA よりも脳卒中 / 全身性塞栓症の減少に有効であった 24-27。本解析で標準用量の NOAC は VKA よりアジア系患者および非アジア系患者の両方に有効であったが、とりわけアジア系患者での成績が優れていた。なお、標準用量の NOAC は非アジア系患者よりもアジア系患者の出血性脳卒中の減少有効であったが、これは VKA による出血リスクがアジア系患者で高いためと考えられる。

過去のメタアナリシスで一貫して明らかにされてきた標準用量の NOAC の主な欠点は、大出血を減少させる効果が弱いことであった 25-27。しかし本解析では標準用量の NOAC は VKA よりアジア系患者に効果があった。非アジア系患者の大出血に対する有益な効果はほとんど認められなかった。国際標準化比 2.0 未満のアジア系患者が多く、3.0 を超えるアジア系患者が少ないにもかかわらず、アジア系患者が VKA により大出血を起こすリスクは一般に非アジア系患者より高いことから、NOAC は非アジア系患者よりもアジア系患者に有効である可能性がある。アジア系患者は NOAC による大出血の絶対リスクが非アジア系患者に比べ数値的に低かった（ダビガトラン 150 mg、リバーオキサバン 20 mg、アビキサバン 5 mg の年間リスクはそれぞれ
図2 標準量のビタミンK拮抗薬（VKA）以外の経口抗凝固薬（NOAC）とVKAの安全性評価項目である大出血（A）、頭蓋内出血（B）、出血性脳卒中（C）、消化管出血（D）の比較。CI：信頼区間、OR：オッズ比。

2.17% vs. 3.52%，3.44% vs. 3.60%，2.02% vs. 2.15%）。したがって、標準用量のNOACにより大出血の絶対リスクが非アジア系患者に比べアジア系患者で一般的に減少した20-23。

標準用量のNOACが抱えるもう1つの重要な批判は、消化管出血リスクの増加である25-28。本研究では消化管出血のリスクの増加は非アジア系患者でのみ有意であった。実際、アジア系患者における消化管出血の件数はROCKET AFでもARISTOTLEでも報告されてなかったが、ROCKET AFでリパロキサンを投与された全患者の消化管出血リスクは、VKAに比べ数値的に高かっ（3.15% vs. 2.16%）20。アスピリンを投与された全患者の消化管出血リスクは、数値的にはVKAと同程度であった（0.78% vs. 0.88%）28。他の出血イベントと違い、VKAによる消化管出血はアジア系患者および非アジア系患者で同程度であった（RE-LYおよびENGAGE AF-TIMI48のアジア系患者と非アジア系患者でそれぞれ1.41% vs. 1.01%および1.11% vs. 1.24%）。

抗血小板薬併用療法は消化管出血の独立した予測因子である29,30。RE-LYのアジア系患者では、非アジア系患者よりも多くアスピリンが併用され、プロトンポンプ阻害薬の使用は少なかったが、ダビガトラム150 mgによる消化管出血の増加は認められなかった25。本研究の結果は、単に消化管出血のリスクがあるというだけでアジア系患者に標準用量のNOACの投与を避けるべきでないことを示唆すると考えられる。

低用量のNOACは、アジア系患者および非アジア系患者の脳卒中／全身性塞栓症の予防においてVKAと同等の効果を持つが、虚性性脳卒中における血栓形成の可能性はより高い。出血性脳卒中に関しては、低用量のNOACはVKAより安全性が高く、アジア系患者と非アジア系患者の差も認められなかった。
図3 低用量のピタミンK拮抗薬（VKA）以外の経口抗凝固薬（NOAC）とVKAの有効性評価項目である脳卒中または全身性塞栓症（A）、虚血性脳卒中（B）、心筋梗塞（C）、全死因による死亡（D）の比較。CI：信頼区間、OR：オッズ比。

は、低用量のNOACがアジア系患者および非アジア系患者の大出血およびICHの低減にVKAより有効であることを示唆する。消化管出血を増加するシグナルははり認められなかった。本解析に基づき、低用量のNOACはアジア系患者に有効かつ安全なVKAの代替薬であり、出血リスクが高い患者では検討するべきである。

最後に、アジア系患者と非アジア系患者でVKAと異なる作用を示すNOACの薬物の一つであるマカロンが有効であることを示す。遺伝的アスキー症候群がVKAに対する感受性が高い傾向にあり、大量投与しやすい、かつ感受性が高い建物の一方であるためVKA代謝の遺伝子多型分布の変動を除くと33,34、アジア系患者は傾向として体重が軽い、心筋梗塞の既往患者の割合が少ない、VKA投与とピタミンK拮抗薬の併用が少ない、脳卒中後遺症・脳卒中既往・非発作性AFの割合が多い、抗血小板薬を使用しているなどの特徴がある31-33。

このような患者背景の差は、民族そのものよりも臨床に関連した抗凝固治療の因子である可能性がある。

研究の限界

本解析にはいくつかの限界がある。第1に、メタアナリシスの対象とした試験から、個人患者レベルのデータが得られなかった。個人患者レベルの情報がないため、本メタアナリシスに記載したアジア諸国で参加した患者の一部が民族的にアジア系患者でない可能性があり、アジア系患者の一部が試験の解析で非アジア系患者集団に組み込まれていた可能性がある21-23。しかし、例えば米国でARIOTILEに組み込まれたアジア系患者は11例のみであったように、アジア系患者の大部分はアジアで参加したと考えられる。また、監督省庁から得た民族および地域レベルの情報に基づく感度分析では、本
図4 低用量のビタミンK拮抗薬（VKA）以外の経口抗凝固薬（NOAC）とVKAの安全性評価項目である大出血（A）、頭蓋内出血（B）、出血性脳卒中（C）、消化管出血（D）の比較。CI：信頼区間、OR：オッズ比。
References


비판막성 심방세동을 가진 아시아 환자에서 뇌졸중 예방을 위한 비-비타민K길항제 경구항응고제의 사용 메타분석

Non–Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Asian Patients With Nonvalvular Atrial Fibrillation
Meta-Analysis

Kang-Ling Wang, MD; Gregory Y. H. Lip, MD; Shing-Jong Lin, MD, PhD; Chern-En Chiang, MD, PhD
(Stroke. 2015;46:2555-2561.)

Key Words: anticoagulants ■ atrial fibrillation ■ hemorrhage ■ stroke

배경과 목적
심방세동 환자에서 뇌졸중 예방을 위하여 사용하는 데 가장 중요한 약물인 비타민 K길항제(vitamin K antagonist)는 심각한 출혈의 위험성 때문에 아시아 국가에서는 충분히 사용되지 않았다. 비-비타민K길항제 경구항응고제(non-VKA oral anticoagulants, NOAC)는 보다 안전한 대체제가 될 수 있다. 이 분석에서 아시아 인종과 비-아시아 인종에서 NOAC의 효과를 비교하였다.

방법
저자들은 3상 임상시험의 통합 데이터에서 아시아 및 비-아시아 국가에서 등록된 환자의 효능 및 안전성을 서로 비교하였다. 대응비( odds ratio, OR [95% 신뢰 구간])는 무작위 효과모델(random effects model)로 계산하였다.

결과
VKA와 비교할 때 표준용량의 NOAC는 비-아시아 국가에 비하여 아시아 국가에서 뇌졸중 및 전신색전증의 발생을 위험성을 더 많이 감소시켰고(OR=0.65 [0.52–0.83] 대 0.85 [0.77–0.93]), 안전성의 측면에서도 주요 출혈 사건의 발생(OR=0.57 [0.44–0.74] 대 0.89 [0.76–1.04], 상호 작용 P=0.004), 출혈뇌졸중(OR=0.32 [0.19–0.52] 대 0.56 [0.44–0.70], 상호 작용 P=0.046)의 발생 위험을 감소시켰다. 또한 위장관 출혈도 아시아 인종에서 더욱 감소되었다(OR=0.79 [0.48–1.32] 대 1.44 [1.12–1.85], 상호 작용 P=0.041), 전반적으로 저용량 NOAC가 아시아 인종 및 비-아시아 인종에서 효능 및 안전성의 이점성 없이 안전하였으나, 허혈뇌졸중, 주요 출혈 및 위장관 출혈에서는 유의하지 않았다.

결론
이 결과는 아시아 인종이 비-아시아 인종에 비하여 표준용량의 NOAC에 활동한 효능 및 안전성을 보임을 확인하였으며, 저용량 NOAC는 두 인종 모두에서 유사한 결과를 보였다.

Figure 2. Safety outcomes of major bleeding (A), intracranial hemorrhage (B), hemorrhagic stroke (C), and gastrointestinal bleeding (D) for the standard-dose non–vitamin K antagonist (VKA) oral anticoagulants (NOACs) vs VKAs. CI indicates confidence interval; and OR, odds ratio.
고혈압 환자에서 뇌졸중 이후 수축기 혈압 조절과 사망률

Systolic Blood Pressure Control and Mortality After Stroke in Hypertensive Patients

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(Stroke. 2015;46:2113-2118.)

Key Words: blood pressure ■ electrocardiography ■ hypertension ■ hypertrophy ■ stroke

배경과 목적
심전도에서 좌심실 비대를 가진 고혈압 환자에서 모든 원인 및 심혈관 사망의 위험이 증가한다. 뇌졸중 이후 혈압(blood pressure, BP)강하는 뇌졸중 재발의 위험을 줄일 수 있지만, 최근 데이터는 뇌졸중 이후 5년째에 측정한 낮은 수축기 혈압(systolic BP, SBP)이 사망률 증가와 관련이 있었다. 고혈압 환자에서 낮은 SBP가 뇌졸중 이후 단기 사망률의 증가와 관련이 있는지 여부는 명확하지 않다.