SUPPLEMENTAL MATERIAL

Non-vitamin K antagonist oral anticoagulants versus warfarin in Asians with atrial fibrillation: meta-analysis of randomized trials and real-world studies

Running title: NOACs in Asian patients with AF

Zhengbiao Xue¹, M.S., Hao Zhang², M.S.

1. Department of Critial Care Medicine, First Affiliated Hospital of Gannan Medical University, Ganzhou, 341000, Jiangxi Province, China
2. Department of Cardiovascular Medicine, Xiangdong Hospital Hunan normal University, Liling, 412200, Hunan Province, China

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SUPPLEMENTAL METHODS

The whole process of this meta-analysis was established according to the Cochrane handbook for systematic reviews.1 We presented the results of this meta-analysis based on the Preferred Reporting Items for Reporting Systematic Reviews and Meta-analyses (PRISMA).2

Literature search

The PubMed and Embase databases were systematically searched with no linguistic restrictions from January 1, 2009 to February 21, 2019 for all studies that comparing the efficacy and safety of any non-vitamin K antagonist oral anticoagulant (NOAC, namely dabigatran, rivaroxaban, edoxaban or apixaban) with warfarin in Asian patients with atrial fibrillation (AF). The search strategy contained a combination of 3 categories of keywords: (1) atrial fibrillation OR non valvular atrial fibrillation; AND (2) non-vitamin K antagonists OR new oral anticoagulants OR novel oral anticoagulants OR direct oral anticoagulants OR oral thrombin inhibitors OR oral factor Xa inhibitors OR dabigatran OR rivaroxaban OR apixaban OR edoxaban; AND (3) vitamin K antagonists OR warfarin. The literature search strategy is shown in Supplemental Table 1. In addition, we further searched the reference lists of previous reviews3-9 to identify the additional studies.

Inclusion and exclusion criteria

We included studies if they satisfied the following criteria: (1) design of the study: randomized clinical trials (RCTs), sub-analyses of RCTs, or observational cohorts (prospective or retrospective); (2) comparisons of the study: the efficacy and safety outcomes of NOACs versus warfarin; (3) study population: Asian patients with nonvalvular AF; and (4) effect estimates of the study: propensity score-matched or adjusted risk ratios (RRs) and 95% confidence intervals (CIs).

Studies were excluded if: (1) they only evaluated AF patients complicating certain specific disease (e.g., coronary artery disease, peripheral arterial disease, chronic kidney disease, hypertension, heart failure, or cancer) or undergoing cardioversion or radiofrequency ablation; and (2) studies were publication types with no data (e.g., reviews, meta-analyses, case reports, editorials, letters, or conference abstracts). In addition, if there was a potentially significant sample overlap among multiple studies, the study with the longest follow-up or highest sample size was selected.

Efficacy and safety outcomes

To assess the efficacy and safety of NOACs versus warfarin, we included the following clinical outcomes: (1) thromboembolic events, including stroke or systemic embolism (SSE), ischemic stroke, and myocardial infarction (MI); (2) major bleeding, intracranial bleeding, and gastrointestinal bleeding; and (3) all-cause death.
Data abstraction

All of the retrieved literatures were screened by 2 reviewers (ZB-X and H-Z) independently. According to the inclusion and exclusion criteria, we first read the titles and abstracts to screen out the potentially available studies, and then reviewed the full texts of these studies in more detail. The disputable issues were discussed with each other. For each included study, we collected the following information: the first author and publication year, design of study, inclusion period, study subjects (age, sex, and number of NOACs or warfarin users), source of patients, types and doses of NOACs, follow-up time, time within therapeutic range (TTR) of warfarin users, and adjusted RRs. If one study reported the adjusted RRs using multiple models, the mostly adjusted one was included.

Quality assessment

According to the Cochrane risk of bias assessment tool, the methodological quality of RCTs was evaluated for the bias risk. This tool involved a total of 7 sections: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The bias risk of each study was scored as ‘low’, ‘unclear’ or ‘high’ risk in each section. We defined ‘low risk’ when 3 out of 5 bias were ‘low’.

For the observational studies, the Newcastle-Ottawa Scale (NOS) tool were applied to evaluate the study quality. This tool involved 3 domains with a total of 9 points: the selection of cohorts (0-4 points), the comparability of cohorts (0-2 points), and the assessment of the outcome (0-3 points). We defined a moderate-to-high quality if an NOS score of ≥ 6 points, and a low quality of an NOS score of < 6 points.

Statistical analysis

All of the statistical analyses were performed by using the Review Manager 5.3 software (the Nordic Cochrane Center, Rigshospitalet, Denmark) and Stata software (version 12.0, Stata Corp LP, College Station, TX). The consistency test was performed using the Cochrane Q test and $I^2$ statistic, where $P < 0.1$ and $I^2 > 50\%$ indicated a substantial heterogeneity, respectively. The natural logarithms of RRs and its standard errors of included studies were calculated, and then pooled by a random-effects model using an inverse variance method. The publication bias was assessed using the funnel plots, and further calculated using the Egger’s and Begg’s tests. In the sensitivity analysis, methods of exclusion of one study at a time or re-analyses with a fixed-effects model were used. We also performed the subgroup analysis based on the age of patients (<65 vs. ≥65 years, or <75 vs. ≥75 years), type ( dabigatran, rivaroxaban, edoxaban, apixaban) or dose (standard dose vs. low dose) of NOACs, and follow-up time (<1 vs. ≥1 year). A value of $P < 0.05$ was considered statistically significant.
Supplementary Table I. Search strategies determined on February 21, 2019

| Databases | Queries | Number of studies |
|-----------|---------|------------------|
| PubMed    | #1      | 62,676           |
|           | atrial fibrillation[Title/Abstract] OR non valvular atrial fibrillation[Title/Abstract] |         |
|           | non-vitamin K antagonists[Title/Abstract] OR new oral anticoagulants[Title/Abstract] OR novel oral anticoagulants[Title/Abstract] OR direct oral anticoagulants[Title/Abstract] OR oral thrombin inhibitors[Title/Abstract] OR oral factor xa inhibitors[Title/Abstract] OR dabigatran[Title/Abstract] OR rivaroxaban[Title/Abstract] OR apixaban[Title/Abstract] OR edoxaban[Title/Abstract] |         |
|           | #2      | 9,315            |
|           | anticoagulants[Title/Abstract] OR oral thrombin inhibitors[Title/Abstract] OR oral factor xa inhibitors[Title/Abstract] OR dabigatran[Title/Abstract] OR rivaroxaban[Title/Abstract] OR apixaban[Title/Abstract] OR edoxaban[Title/Abstract] |         |
|           | #3      | 25,368           |
|           | vitamin K antagonists[Title/Abstract] OR warfarin[Title/Abstract] |         |
|           | #4      | 2,609            |
|           | #1 and #2 and #3 and From 01/01/2009 to present |         |
| EMBASE    | #1      | 109,188          |
|           | 'atrial fibrillation':ab,ti OR 'non valvular atrial fibrillation':ab,ti |         |
|           | 'non-vitamin K antagonists':ab,ti OR 'new oral anticoagulants':ab,ti OR 'novel oral anticoagulants':ab,ti OR 'direct oral anticoagulants':ab,ti |         |
|           | #2      | 17,392           |
|           | anticoagulants':ab,ti OR 'oral thrombin inhibitors':ab,ti OR 'oral factor Xa inhibitors':ab,ti OR 'dabigatran':ab,ti OR 'rivaroxaban':ab,ti OR 'apixaban':ab,ti OR 'edoxaban':ab,ti |         |
|           | #3      | 40,780           |
|           | 'vitamin K antagonists':ab,ti OR 'warfarin':ab,ti |         |
|           | #4      | 4,956            |
|           | #1 and #2 and #3 and From 01/01/2009 to present |         |
## Supplementary Table II. Studies for exclusion and inclusion after reviewed in the full-texts

| Study Items |
|-------------|
| **Studies for exclusion (n=39)** |
| 1. Shimokawa H, Yamashita T, Uchiyama S, Kitazono T, Shimizu W, Ikeda T, Kamouchi M, Kaikita K, Fukuda K, Origasa H, Sakuma I, Saku K, Okumura Y, Nakamura Y, Morimoto H, Matsumoto N, Tsuchida A, Ako J, Sugishita N, Shimizu S, Atariashi H, Inoue H. The EXPAND study: Efficacy and safety of rivaroxaban in Japanese patients with non-valvular atrial fibrillation. *INT J CARDIOL*. 2018;258:126-132. |
| 2. Okumura Y, Yokoyama K, Matsumoto N, Tachibana E, Kuronuma K, Oiwa K, Matsumoto M, Kojima T, Hanada S, Nomoto K, Arima K, Takahashi F, Kotani T, Ikeya Y, Fukushima S, Itoh S, Kondo K, Chiku M, Ohno Y, Onikura M, Hirayama A, The SARI. Current use of direct oral anticoagulants for atrial fibrillation in Japan: Findings from the SAKURA AF Registry. *Journal of Arrhythmia*. 2017;33(4):289-296. |
| 3. Chan LX, Wong YM, Chia P, Kek ZL. A single institution’s experience with using dabigatran, rivaroxaban and warfarin for prevention of thromboembolism in atrial fibrillation. *Proceedings of Singapore Healthcare*. 2017;27(1):20-25. |
| 4. Yap SH, Ng YP, Roslan A, Kolanthaivelu J, Koh KW, P’Ng HS, Boo YL, Hoo FK, Yap LB. A comparison of dabigatran and warfarin for stroke prevention in elderly Asian population with nonvalvular atrial fibrillation: An audit of current practice in Malaysia. *The Medical Journal of Malaysia*. 2017;72(6):360. |
| 5. Verdeccia P, D’Onofrio A, Russo V, Fedele F, Adamo F, Benedetti G, Ferrante F, Lodigiani C, Pucillulo F, Di Lenarda A, Mazzone C, Iorio A. Real-world evidence on safety and effectiveness of a novel oral anticoagulant for the treatment of atrial fibrillation: A retrospective analysis in five Italian districts. *Giornale Italiano di Cardiologia*. 2017;18(10):e26. |
| 6. Kwon CH, Kim M, Kim J, Nam GB, Choi KJ, Kim YH. Real-world comparison of non-vitamin K antagonist oral anticoagulants and warfarin in Asian octogenarian patients with atrial fibrillation. *J GERIATR CARDIOL*. 2016;13(7):566-572. |
| **Warfarin not as controls (n=13)** |
| 2. Kim YH, Shim J, Tsai CT, Wang CC, Vilela G, Muengtaweepongs A, Kurniawan M, Maskon O, Li Fern H, Nguyen TH, Thanachartwat T, Sim K, Camm AJ. XANAP: A real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation in Asia. *J Arrhythm*. 2018;34(4):418-427. |
| 3. Bando S, Nishikado A, Hiura N, Ikeda S, Kakutani A, Yamamoto K, Kaname N, Fukatani M, Takagi Y, Yukiiri K, Fukuda Y, Nakaya Y. Efficacy and safety of rivaroxaban in extreme elderly patients with atrial fibrillation: Analysis of the Shikoku Rivaroxaban Registry Trial (SRRT). *J CARDIOL*. 2018;71(2):197-201. |
| 4. Chan Y, Yeh Y, Tu H, Kuo C, Chang S, Wu L, Lee H, See L. Bleeding risk with dabigatran, rivaroxaban, warfarin, and antiplatelet agent in Asians with non-valvular atrial fibrillation: Findings from the SAKURA AF Registry. *Cardiology*. 2017;27(1):20-25. |
| **No adjusted data (n=6)** |
| 1. Shimokawa H, Yamashita T, Uchiyama S, Kitazono T, Shimizu W, Ikeda T, Kamouchi M, Kaikita K, Fukuda K, Origasa H, Sakuma I, Saku K, Okumura Y, Nakamura Y, Morimoto H, Matsumoto N, Tsuchida A, Ako J, Sugishita N, Shimizu S, Atariashi H, Inoue H. The EXPAND study: Efficacy and safety of rivaroxaban in Japanese patients with non-valvular atrial fibrillation. *INT J CARDIOL*. 2018;258:126-132. |
fibrillation. *Oncotarget.* 2017;8(58):98898-98917.

5. Kodani E, Atarashi H, Inoue H, Okumura K, Yamashita T, Origasa H. Beneficial Effect of Non-Vitamin K Antagonist Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation – Results of the J-RHYTHM Registry 2 –. *CIRC J.* 2016;80(4):843-851.

6. Ho CW, Ho MH, Chan PH, Hai JJ, Cheung E, Yeung CY, Lau KK, Chan KH, Lau CP, Lip GY, Leung GK, Tse HF, Siu CW. Ischemic stroke and intracranial hemorrhage with aspirin, dabigatran, and warfarin: impact of quality of anticoagulation control. *STROKE.* 2015;46(1):23-30.

7. Arbel R, Sergienko R, Hammerman A, Greenberg-Dotan S, Batat E, Avnery O, Ellis MH. EFFECTIVENESS AND SAFETY OF OFF-LABEL DOSE-REDUCED DIRECT ORAL ANTICOAGULANTS IN ATRIAL FIBRILLATION. *AM J MED.* 2019.

8. Lin Y, Chien S, Hsieh Y, Shih C, Lin F, Tsao N, Chen C, Kao Y, Chiang K, Chen W, Chien L, Huang C. Effectiveness and Safety of Standard- and Low-Dose Rivaroxaban in Asians With Atrial Fibrillation. *J AM COLL CARDIOL.* 2018;72(5):477-485.

9. Lai CL, Chen HM, Liao MT, Lin TT, Chan KA. Comparative Effectiveness and Safety of Dabigatran and Rivaroxaban in Atrial Fibrillation Patients. *J AM HEART ASSOC.* 2017;6(4).

10. Wu S, Xie S, Xu Y, Que D, Yau TO, Wang L, Huang Y. Persistence and outcomes of non-vitamin K antagonist oral anticoagulants versus warfarin in patients with non-valvular atrial fibrillation. *J CLIN NURS.* 2019.

11. Jeong HK, Lee KH, Park HW, Yoon NS, Kim MC, Lee N, Kim JS, Ahn Y, Jeong MH, Park JC, Cho JG. Real World Comparison of Rivaroxaban and Warfarin in Korean Patients with Atrial Fibrillation: Propensity Matching Cohort Analysis. *Chonnam Med J.* 2019;55(1):54-61.

12. Yokoyama S, Tanaka Y, Nakagita K, Hosomi K, Takada M. Bleeding Risk of Warfarin and Direct Oral Anticoagulants in Younger Population: A Historical Cohort Study Using a Japanese Claims Database. *INT J MED SCI.* 2018;15(14):1686-1693.

13. Ellis MH, Neuman T, Bitterman H, Dotan SG, Hammerman A, Battat E, Eikelboom JW, Ginsberg JS, Hirsh J. Bleeding in patients with atrial fibrillation treated with dabigatran, rivaroxaban or warfarin: A retrospective population-based cohort study. *EUR J INTERN MED.* 2016;33:55-59.

1. Geng Y, Lan D, Liu N, Du X, Zheng D, Tang R, Long D, Yu R, Sang C, Bai R, Jiang C, Li S, Guo X, Wang W, Xia S, Chang S, Dong J, Chen A, Ma C. Patient-Reported Treatment Satisfaction with Dabigatran versus Warfarin in Patients with Non-Valvular Atrial Fibrillation in China. *THROMB HAEMOSTASIS.* 2018;118(10):1815-1822.

2. Okumura Y, Yokoyama K, Matsumoto N, Tachibana E, Kuronuma K, Oiwa K, Matsumoto M, Kojima T, Arima K, Kotani T, Nomoto K, Ikeya Y, Fukushima S, Onikura M, Suzuki Y, Fujita M, Ando H, Ishikawa N, Hirayama A. Patient Satisfaction with Direct Oral Anticoagulants and Warfarin. *INT HEART J.* 2018;59(6):1266-1274.

3. Naganuma M, Shiga T, Nagao T, Maruyama K, Suzuki A, Murasaki K, Hagiwara N. Renal function and treatment persistence with non-Vitamin K antagonist oral anticoagulants in Japanese patients with atrial fibrillation: A single-center experience. *Japanese Journal of Clinical Pharmacology and Therapeutics.* 2016;47(3):115-122.

4. Shiga T, Naganuma M, Nagao T, Maruyama K, Suzuki A, Murasaki K, Hagiwara N. Persistence of non-vitamin K antagonist oral anticoagulant use in Japanese patients with atrial fibrillation: A single-center observational study. *Journal of Arrhythmia.* 2015;31(6):339-344.

5. Uchiyama S, Hori M, Matsumoto M, Tanahashi N, Momomura S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, Ueda H, Iekushi K, Yamanaka S, Tajiri M. Net

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No efficacy and safety outcomes (n=7)
Clinical Benefit of Rivaroxaban versus Warfarin in Japanese Patients with Nonvalvular Atrial Fibrillation: A Subgroup Analysis of J-ROCKET AF. Journal of Stroke and Cerebrovascular Diseases. 2014;23(5):1142-1147.

6. Chan Y, Yeh Y, Hsieh M, Chang C, Tu H, Chang S, See L, Kuo C, Kuo C. The risk of acute kidney injury in Asians treated with apixaban, rivaroxaban, dabigatran, or warfarin for non-valvular atrial fibrillation: A nationwide cohort study in Taiwan. INT J CARDIOL. 2018;265:83-89.

7. Chan YH, Yeh YH, See LC, Wang CL, Chang SH, Lee HF, Wu LS, Tu HT, Kuo CT. Acute Kidney Injury in Asians With Atrial Fibrillation Treated With Dabigatran or Warfarin. J AM COLL CARDIOL. 2016;68(21):2272-2283.

Combined efficacy or safety outcomes (n=1)

1. Chan Y, Lee K, Kao Y, Huang C, Chen Y, Hang SC, Chu P. The comparison of non-vitamin K antagonist oral anticoagulants versus well-managed warfarin with a lower INR target of 1.5 to 2.5 in Asians patients with non-valvular atrial fibrillation. PLOS ONE. 2019;14(3):e213517.

2. Lee S, Choi E, Park CS, Han K, Jung J, Oh S, Lip GYH. Direct Oral Anticoagulants in Patients With Nonvalvular Atrial Fibrillation and Low Body Weight. J AM COLL CARDIOL. 2019;73(3):210-217.

3. Lee H, Chan Y, Tu H, Kuo C, Yeh Y, Chang S, Wu L, See L. The effectiveness and safety of low-dose rivaroxaban in Asians with non-valvular atrial fibrillation. INT J CARDIOL. 2018;261:78-83.

4. Chao T, Liu C, Lin Y, Chang S, Lo L, Hu Y, Tuan T, Liao J, Chung F, Chen T, Lip GYH, Chen S. Oral Anticoagulation in Very Elderly Patients With Atrial Fibrillation. CIRCULATION. 2018;138(1):37-47.

5. Lau WC, Li X, Wong IC, Chan EW. Bleeding-related hospital admissions and 30-day readmissions in patients with non-valvular atrial fibrillation treated with dabigatran versus warfarin. Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research. 2017;20(5):A263.

6. Chan Y, Kuo C, Yeh Y, Chang S, Wu L, Lee H, Tu H, See L. Thromboembolic, Bleeding, and Mortality Risks of Rivaroxaban and Dabigatran in Asians With Nonvalvular Atrial Fibrillation. J AM COLL CARDIOL. 2016;68(13):1389-1401.

7. Yamashita T, Koretsune Y, Yang Y, Chen SA, Chang N, Shimada YJ, Kimura T, Miyazaki K, Abe K, Mercuri M, Ruff CT, Giugliano RP. Edoxaban vs. Warfarin in East Asian Patients With Atrial Fibrillation- An ENGAGE AF-TIMI 48 Subanalysis. CIRC J. 2016;80(4):860-869.

8. Shimada YJ, Yamashita T, Koretsune Y, Kimura T, Abe K, Sasaki S, Mercuri M, Ruff CT, Giugliano RP. Effects of Regional Differences in Asia on Efficacy and Safety of Edoxaban Compared With Warfarin--Insights From the ENGAGE AF-TIMI 48 Trial. CIRC J. 2015;79(12):2560-2567.

9. Horii M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, Ueda H, Iekushi K, Yamanaka S, Tajiri M. Rivaroxaban versus Warfarin in Japanese Patients with Nonvalvular Atrial Fibrillation in Relation to the CHADS2 Score: A Subgroup Analysis of the J-ROCKET AF Trial.
10. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, Ueda H, Iekushi K, Yamanaka S, Tajiri M. Rivaroxaban vs. warfarin in Japanese patients with non-valvular atrial fibrillation in relation to age. CIRC J. 2014;78(6):1349-1356.

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12. Hori M, Connolly SJ, Ezekowitz MD, Reilly PA, Yusuf S, Wallentin L. Efficacy and safety of dabigatran vs. warfarin in patients with atrial fibrillation--sub-analysis in Japanese population in RE-LY trial. CIRC J. 2011;75(4):800-805.

Studies for inclusion (n=26)

RCTs (n=5)

1. Chao T, Chen S, Ruff CT, Hamershock RA, Mercuri MF, Antman EM, Braunwald E, Giugliano RP. Clinical outcomes, edoxaban concentration, and anti-factor Xa activity of Asian patients with atrial fibrillation compared with non-Asians in the ENGAGE AF-TIMI 48 trial. EUR HEART J. 2018.

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3. Goto S, Zhu J, Liu L, Oh BH, Woydyla DM, Aylward P, Bahit MC, Gersh BJ, Hanna M, Horowitz J, Lopes RD, Wallentin L, Xavier D, Alexander JH. 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(3):303-309.

4. Hori M, Connolly SJ, Zhu J, Liu LS, Lau CP, Pais P, Xavier D, Kim SS, Omar R, Dans AL, Tan RS, Chen JH, Tanomsup S, Watanabe M, Koyanagi M, Ezekowitz MD, Reilly PA, Wallentin L, Yusuf S. Dabigatran versus warfarin: effects on ischemic and hemorrhagic strokes and bleeding in Asians and non-Asians with atrial fibrillation. STROKE. 2013;44(7):1891-1896.

5. Hori M, Matsumoto M, Tanahashi N, Momomura S, Uchiyama S, Goto S, Izumi T, Koretsune Y, Kajikawa M, Kato M, Ueda H, Iwamoto K, Tajiri M. Rivaroxaban vs. warfarin in Japanese patients with atrial fibrillation - the J-ROCKET AF study -. CIRC J. 2012;76(9):2104-2111.

Observational studies (n=21)

1. Koretsune Y, Yamashita T, Yasaka M, Ono Y, Hirakawa T, Ishida K, Kuroki D, Sumida T, Urushihara H. Comparative effectiveness and safety of warfarin and dabigatran in patients with non-valvular atrial fibrillation in Japan: A claims database analysis. J CARDIOL. 2019;73(3):204-209.

2. Okumura Y, Yokoyama K, Matsumoto N, Tachibana E, Kuronuma K, Oiwa K, Matsumoto M, Kojima T, Hanada S, Nomoto K, Arima K, Takahashi F, Kotani T, Ikeya Y, Fukushima S, Itou S, Kondo K, Chiku M, Ohno Y, Onikura M, Hirayama A. Three-Year Clinical Outcomes Associated With Warfarin vs. Direct Oral Anticoagulant Use Among Japanese Patients With Atrial Fibrillation — Findings From the SAKURA AF Registry —. CIRC J. 2018;82(10):2500-2509.

3. Chan YH, See LC, Tu HT, Yeh YH, Chang SH, Wu LS, Lee HF, Wang CL, Kuo CF, Kuo CT. Efficacy and Safety of Apixaban, Dabigatran, Rivaroxaban, and Warfarin in
Asians With Nonvalvular Atrial Fibrillation. J AM HEART ASSOC. 2018;7(8).
4. Huang H, Lin S, Cheng S, Wang C. Effectiveness and Safety of Different Rivaroxaban Dosage Regimens in Patients with Non-Valvular Atrial Fibrillation: A Nationwide, Population-Based Cohort Study. SCI REP-UK. 2018;8(1).
5. Lee SR, Choi EK, Han KD, Jung JH, Oh S, Lip GYH. Edoxaban in Asian Patients With Atrial Fibrillation: Effectiveness and Safety. J AM COLI CARDIOL. 2018;72(8):838-853.
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8. Kohsaka S, Katada J, Saito K, Terayama Y. Safety and effectiveness of apixaban in comparison to warfarin in patients with nonvalvular atrial fibrillation: a propensity-matched analysis from Japanese administrative claims data. CURR MED RES OPIN. 2018;34(9):1627-1634.
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11. Li WH, Huang D, Chiang CE, Lau CP, Tse HF, Chan EW, Wong I, Lip G, Chan PH, Siu CW. Efficacy and safety of dabigatran, rivaroxaban, and warfarin for stroke prevention in Chinese patients with atrial fibrillation: the Hong Kong Atrial Fibrillation Project. CLIN CARDIOL. 2017;40(4):222-229.
12. Yamashita Y, Uozumi R, Hamatani Y, Esato M, Chen Y, Tsuji H, Wada H, Hasegawa K, Ogawa H, Abe M, Morita S, Akao M. Current Status and Outcomes of Direct Oral Anticoagulant Use in Real-World Atrial Fibrillation Patients — Fushimi AF Registry —. CIRC J. 2017;81(9):1278-1285.
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14. Kohsaka S, Murata T, Izumi N, Katada J, Wang F, Terayama Y. Bleeding risk of apixaban, dabigatran, and low-dose rivaroxaban compared with warfarin in Japanese patients with non-valvular atrial fibrillation: a propensity matched analysis of administrative claims data. CURR MED RES OPIN. 2017;33(11):1955-1963.
15. Naganuma M, Shiga T, Nagao T, Suzuki A, Murasaki K, Hagiwara N. Effectiveness and safety of dabigatran versus warfarin in “real-world” Japanese patients with atrial fibrillation: A single-center observational study. Journal of Arrhythmia. 2017;33(2):107-110.
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Fibrillation. *STROKE.* 2016;47(2):441-449.

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Supplementary Table III. Baseline characteristics of the included studies

| Studies               | Study design              | Inclusion period | Source of patients          | Mean age (y)/Sex | NOACs used | Number of NOACs users | Follow-up time of NOACs users (y) | Number of warfarin users | Follow-up time of warfarin users (y) |
|-----------------------|---------------------------|------------------|-----------------------------|------------------|------------|-----------------------|-----------------------------------|--------------------------|-------------------------------------|
| Chao T-2018           | Sub-analysis of RCT trial | -                | ENGAGE AF-TIMI 48           | 68.7/Both        | EDO        | 1,942                 | 2.8*                              | 967                      | 2.8*                                |
| Wong KS-2014          | Sub-analysis of RCT trial | -                | ROCKET AF                   | 70.0/Both        | RIV        | 468                   | 1.83                              | 464                      | 1.94                                |
| Goto S-2014           | Sub-analysis of RCT trial | -                | ARISTOTLE                   | 69.0/Both        | API        | 988                   | 1.8*                              | 1,005                    | 1.8*                                |
| Hori M-2013           | Sub-analysis of RCT trial | -                | RE-LY                       | 68.0/Both        | DA         | 1,856                 | 2.0*                              | 926                      | 2.0*                                |
| Hori M-2012           | Sub-analysis of RCT trial | -                | J-ROCKET AF                 | 71.1/Both        | RIV        | 639                   | 30 d                              | 639                      | 30 d                                |
| Koretsune Y-2019      | Retrospective cohort      | 03/2011-06/20    | Medical Data Vision         | 73.5/Both        | DA         | 4,606                 | 0.6                               | 4,606                    | 0.5                                 |
|                       |                           | 16               | Database (Japan)            |                  |            |                       |                                   |                          |                                     |
| Kim HM-2019           | Retrospective cohort      | 01/2012-06/20    | Hospital-based AF database  | 83.4/Both        | DA, RIV, API| 403                   | 0.46                              | 284                      | 1.28                                |
|                       |                           | 16               | (Korea)                     |                  |            |                       |                                   |                          |                                     |
| Okumura Y-2018        | Prospective cohort        | 09/2013-12/20    | SAKURA AF Registry          | 72.0/Both        | RVI, API   | 761                   | 2.0                               | 1,561                    | 3.0                                 |
|                       |                           | 15               | (Japan)                     |                  |            |                       |                                   |                          |                                     |
| Study          | Type          | Date Range       | Database Details                                                                 | DA | RIV | API | RVI  |
|---------------|---------------|------------------|--------------------------------------------------------------------------------|----|-----|-----|------|
| Chan YH-2018  | Retrospective | 06/2012-12/20    | National Health Insurance Research Database (China, Taiwan)                     | 5,843 | 20,079 | 27,777 | 19,375 | 1.47 |
| Kohsaka S-2018| Retrospective | 03/2011-06/20    | Medical Data Vision Database (Japan)                                             | 11,972 | NA | NA | NA |
| Cho MS-2018   | Retrospective | 07/2015-12/20    | National Health Insurance Service (Korea)                                       | 21,000 | 1.25 | 10,409 | 1.25 |
| Lee SR-2018   | Retrospective | 01/2014-12/20    | National Health Insurance Service (Korea)                                       | 4,061 | 0.3 | 12,183 | 0.9 |
| Law S-2018    | Retrospective | 2010-2015        | Hong Kong clinical database (China, Hong Kong)                                 | 4,903 | 1.23 | 4,903 | 1.23 |
| Lai CL-2018   | Retrospective | 06/2011-05/20    | National Health Insurance Research Database (China, Taiwan)                     | 1,180 | 0.5 | 1,497 | 0.5 |
| Huang HY-2018 | Retrospective | 06/2012-12/20    | National Health Insurance Research Database (China, Taiwan)                     | 9,637 | 0.96 | 9,637 | 1.18 |
| Wang CL-2018  | Retrospective | 2010-2017        | Hospital-based AF registry (China, Taiwan)                                      | 1,788 | 3,596 | 1,674 | NA |
| Cha MJ-2017   | Prospective   | 01/2014-12/20    | National Health Insurance Service database (Korea)                             | 11,611 | 0.50 | 23,222 | 1.51 |
| Kohsaka S-2017| Retrospective | 03/2011-03/20    | Medical Data Vision database (Japan)                                            | 5,977 | 5,090 | 6,726 | 1.0 |
| Study          | Type               | Start/End Date | Location                              | AF (%) | NOAC (%) | TTR (y) | DA (x1000) | RA (y) |
|---------------|--------------------|----------------|---------------------------------------|--------|----------|---------|------------|--------|
| Naganuma M-2017 | Retrospective cohort | 03/2011-12/20 13 | Tokyo Hospital-based AF registry (Japan) | 69.0/Both | DA 181 | 1.3 | 181 | 1.3 |
| Li WH-2017    | Prospective cohort  | 01/2008-12/20 14 | Hospital-based AF registry (China, Hong Kong) | 73.1/Both | DA 467 | 1.8 | 157 | 1.8 |
| Yamashita Y-2017 | Prospective cohort | 03/2011-11/20 15 | Fushimi AF Registry (Japan) | 74.0/Both | DA 115 | 222 | RVI | 3.0 |
| Lee KH -2017 | Retrospective cohort | 01/2012-12/20 13 | Hospital-based AF registry (Korea) | 70.6/Both | DA 549 | 1.0 | 549 | 1.0 |
| Chan YH-2016 | Retrospective cohort | 06/2012-12/20 13 | National Health Insurance Research Database (China, Taiwan) | 75.5/Both | DA 9,940 | 0.67 | 9,913 | 0.67 |
| Yap LB-2016 | Retrospective cohort | 01/2009-12/20 13 | National Heart Institute (Malaysia) | 66.1/Both | DA 500 | 0.9 | 500 | 0.7 |
| Chan PH-2016 | Retrospective cohort | 2010-2013       | Hospital-based AF registry (China, Hong Kong) | 84.7/Both | DA 129 | 1.0 | 342 | 1.0 |
| Ho JC-2012    | Retrospective cohort | 01/2010-11/20 11 | Hospital-based AF registry (China, Hong Kong) | 70.1/Both | DA 122 | NA | 122 | 2.6 |

AF=atrial fibrillation; NOACs=non-vitamin K antagonist oral anticoagulants; RCT=randomized controlled trial; DA=dabigatran; RIV=rivaroxaban; API=apixaban; EDO=edoxaban; TTR=time within therapeutic range; y=years; d=days; NA=not available.

*the follow-up time of the original NOAC trials.
**Supplementary Table IV. Risk of bias assessment for randomized clinical trials**

| Study           | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias | Total* |
|-----------------|---------------------------------------------|----------------------------------------|----------------------------------------------------------|-------------------------------------------------|----------------------------------------|-------------------------------------|-----------|--------|
| Chao T-2018     | Low risk                                   | Low risk                               | Low risk                                                 | Low risk                                        | Low risk                               | Low risk                            | Low       | Low    |
| Wong KS-2014    | Low risk                                   | Low risk                               | Low risk                                                 | Low risk                                        | Low risk                               | Low risk                            | Low       | Low    |
| Goto S-2014     | Low risk                                   | Low risk                               | Low risk                                                 | Low risk                                        | Low risk                               | Low risk                            | Low       | Low    |
| Hori M-2013     | Low risk                                   | Low risk                               | Low risk                                                 | Low risk                                        | Low risk                               | Low risk                            | Low       | Low    |
| Hori M-2012     | Low risk                                   | Low risk                               | Low risk                                                 | Low risk                                        | Low risk                               | Low risk                            | Low       | Low    |

*We defined as “low risk” when 3 out of 5 bias were “low”.*
### Supplementary Table V. Quality assessment for the included observational studies

| Included studies    | Representativeness of Exposed Cohort | Selection of Non-Exposed Cohort | Ascertainment of Exposure | Demonstration That Outcome of Interest Was Not Present at Start of Study | Adjust for the important Risk factors | Adjust for other risk factors | Assessment of Outcome | Follow-up length | Loss to follow-up rate | Total points * |
|---------------------|--------------------------------------|---------------------------------|---------------------------|--------------------------------------------------------------------------|----------------------------------------|----------------------------|----------------------|------------------|------------------------|-----------------|
| Koretsune Y-2019    | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Kim HM-2019         | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 7               |
| Okumura Y-2018      | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Chan YH-2018        | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Huang H-2018        | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Lee SR-2018         | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 9               |
| Law S-2018          | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Lai CL-2018         | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 6               |
| Kohsaka S-2018      | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Cho MS-2018         | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Wang CL-2018        | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 6               |
| Li WH-2017          | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Yamashita Y-2017    | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Cha MJ-2017         | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 9               |
| Kohsaka S-2017      | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Naganuma M-2017     | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Lee KH-2017         | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Chan YH-2016        | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
| Yap LB-2016         | ※                                   | ※                              | ※                         | ※                                                                         | ※                                      | ※                         | ※                   | ※                | ※                      | 8               |
The Newcastle-Ottawa Scale (NOS) items, with a total score of 9 points, were used to evaluate the quality of the observational studies, which involve the selection of cohorts (0-4 points), the comparability of cohorts (0-2 points), and the assessment of the outcome (0-3 points).
Supplementary Figure I Flowchart of electronic retrievals in this meta-analysis
Supplementary Figure II. Comparing the efficacy outcomes of NOACs with warfarin in Asians with AF based on RCTs.

AF=atrial fibrillation; NOACs=non-vitamin K antagonist oral anticoagulants; RCT=randomized controlled trial; SSE=stroke or systemic embolism; CI=confidence interval; SE=standard error; IV=inverse of the variance.
Supplementary Figure III. Comparing the safety outcomes of NOACs with warfarin in Asians with AF based on RCTs.

AF=atrial fibrillation; NOACs=non-vitamin K antagonist oral anticoagulants; RCT=randomized controlled trial; SSE=stroke or systemic embolism; CI=confidence interval; SE=standard error; IV=inverse of the variance.
**Supplementary Figure IV.** Comparing the ischemic stroke of NOACs with warfarin in real-world Asians with AF.

AF=atrial fibrillation; NOACs=non-Vitamin K antagonist oral anticoagulants; DA=dabigatran; RIV=rivaroxaban; IS=ischemic stroke; CI=confidence interval; SE=standard error; IV=inverse of the variance.
Supplementary Figure V. Comparing the myocardial infarction of NOACs with warfarin in real-world Asians with AF.

AF=atrial fibrillation; NOACs=non-Vitamin K antagonist oral anticoagulants; DA=dabigatran; RIV=rivaroxaban; API=apixaban; CI=confidence interval; SE=standard error; IV=inverse of the variance.

| Study or Subgroup         | log(Risk Ratio) | SE  | Weight | IV, Random, 95% CI          | Risk Ratio IV, Random, 95% CI |
|---------------------------|-----------------|-----|--------|-----------------------------|--------------------------------|
| Chan YH-2016              | -0.4            | 0.228 | 27.2%  | 0.67 [0.43, 1.05]           |                                |
| Chan YH-2018/API          | -0.274          | 0.269 | 21.1%  | 0.76 [0.46, 1.26]           |                                |
| Chan YH-2018/DA           | -0.248          | 0.231 | 26.6%  | 0.78 [0.50, 1.23]           |                                |
| Chan YH-2018/RIV          | -0.386          | 0.246 | 23.3%  | 0.68 [0.42, 1.10]           |                                |
| Lee KH-2017[high dose]    | 0.708           | 1.139 | 1.1%   | 2.03 [0.22, 18.92]          |                                |
| Lee KH-2017[low dose]     | 1.151           | 1.277 | 0.9%   | 3.16 [0.20, 38.02]          |                                |

Total (95% CI) 100.0% 0.74 [0.58, 0.93]

Heterogeneity: Tau² = 0.00; Chi² = 2.45, df = 5 (P = 0.78), I² = 0%

Test for overall effect: Z = 2.56 (P = 0.01)
Supplementary Figure VI. Comparing the gastrointestinal bleeding of NOACs with warfarin in real-world Asians with AF.

AF=atrial fibrillation; NOACs=non-vitamin K antagonist oral anticoagulants; DA=dabigatran; RIV=rivaroxaban; API=apixaban; EDO=edoxaban; CI=confidence interval; SE=standard error; IV=inverse of the variance.
Supplementary Figure VII. Funnel plots of the reported efficacy and safety outcomes for randomized clinical trials.

RR=risk ratio; SE=standard error.
Supplementary Figure VIII. Funnel plots of the reported outcomes for observational studies: (A) ischemic stroke or systemic embolism; (B) ischemic stroke; (C) all-cause death; (D) major bleeding; (E) intracranial bleeding; and (F) gastrointestinal bleeding.

RR = risk ratio; SE = standard error.
Supplementary Figure IX. Egger’s and Begg’s tests of the reported outcomes for observational studies: (A) ischemic stroke or systemic embolism; (B) ischemic stroke; (C) all-cause death; (D) major bleeding; (E) intracranial bleeding; and (F) gastrointestinal bleeding.
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