Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Asians With Nonvalvular Atrial Fibrillation

A Network Meta-Analysis

Xiong, Qinmei; Wang, Cen; Liu, Hualong; Tan, Zhaochong; Chen, Chen; Li, Juxiang; Lip, Gregory Y H; Hong, Kui

Published in:
Clinical and Applied Thrombosis/Hemostasis

DOI (link to publication from Publisher):
10.1177/1076029619885188

Publication date:
2019

Document Version
Publisher's PDF, also known as Version of record

Original Article

Clinical and Applied Thrombosis/Hemostasis
Volume 25: 1-8

DOI: 10.1177/1076029619885188
journals.sagepub.com/home/cat
SAGE

Efficacy and Safety of Non-Vitamin K Antagonist Oral Anticoagulants in Asians With Nonvalvular Atrial Fibrillation: A Network Meta-Analysis

Qinmei Xiong, MD, PhD[1], Cen Wang, MD[1], Hualong Liu, MD[1], Zhaochong Tan, MD[1], Chen Chen, MD[1], Juxiang Li, MD[1], Gregory Y. H. Lip, MD[2,3], and Kui Hong, MD, PhD[1,4]

Abstract

There are few head-to-head trials directly comparing non-vitamin K antagonist oral anticoagulants (NOACs) against one other. A network meta-analysis (NMA) was performed to examine the indirect comparisons among NOACs in Asians with nonvalvular atrial fibrillation (NVAF). STATA 15.0 and ADDIS 1.16.8 softwares were used to perform the statistical analysis. Odds ratios with 95% credible intervals were applied to evaluate the end points. The probabilities of treatment rank were used to understand which interventions are more effective and safe, and the total rank probability was 1. In our NMA, the rank probabilities of apixaban in the case of stroke or systemic embolism, death from any cause, major bleeding, and intracranial hemorrhage (ICH) were 0.47, 0.49, 0.42, and 0.51, respectively. For cases of myocardial infarction, the rank probabilities of rivaroxaban were 0.40. This NMA indirectly compares the main efficacy and safety end points among NOACs in Asians with NVAF, and the rank probability analysis showed that apixaban likely performs best in cases of stroke or systemic embolism, death from any cause, and ICH; rivaroxaban may have the best performance for myocardial infarction.

Keywords

atrial fibrillation, Asian, NOACs, indirect comparison, network meta-analysis

Date received: 10 July 2019; revised: 16 September 2019; accepted: 01 October 2019.

Introduction

Patients with nonvalvular atrial fibrillation (NVAF) are at increased risk of stroke and death.[1,2] Warfarin, one of the Vitamin K antagonists, is an effective therapy in preventing stroke or systemic embolism for patients with NVAF.[3-5] However, there are some limitations for underuse of warfarin in clinical practice, such as a narrow therapeutic range and multiple interactions with food and drugs, requiring frequent laboratory coagulation monitoring and dose adjustments. Thus, several non-vitamin K antagonist oral anticoagulants (NOACs) have been developed and validated in large randomized trials, compared to warfarin.[6-9] All of the 4 NOACs have been confirmed to be superior or at least noninferior to warfarin in preventing stroke or systemic embolism, with lower rates of bleeding and mortality.[6-9]

Many studies have shown that warfarin is more underused in East Asia versus other regions of the world.[10] The effect of NOACs in Asian NVAF populations has been recently evaluated, including a number of real-world studies.[11-19] In randomized trials, the NOACs appear to have greater efficacy and better safety in Asians compared to non-Asians.[20] The lower body weight and body mass index (BMI) in Chinese

[1] Cardiovascular Department, the Second Affiliated Hospital of Nanchang University, Jiangxi, China
[2] Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom
[3] Aalborg Thrombosis Research Unit, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[4] Jiangxi Key Laboratory of Molecular Medicine, Jiangxi, China

Corresponding Author:
Kui Hong, Cardiovascular Department, the Second Affiliated Hospital of Nanchang University, Jiangxi, 330006, China.
Email: hongkui88@163.com

populations might be associated with the efficacy and safety of NOACs.[21,22]

Nevertheless, there are no head-to-head trials conducted to directly compare these NOACs against each other. An indirect comparison analysis on comparing the efficacy and safety of edoxaban to other agents has been recently published[23] but did not focus on Asian patients. In Asia, clinicians and patients are interested in identifying which of the NOACs performs better among Asian patients with NVAF. We performed a systematic review and network meta-analysis (NMA) to compare the efficacy and safety of these 4 NOACs compared to each other, based on Asian data.

Methods

Inclusion and Exclusion Criteria

The following inclusion criteria were applied for selecting studies: (1) Types of studies: clinical studies focusing on the efficacy and safety of NOACs among Asian NVAF patients; (2) Participants: anticoagulated Asians with NVAF; and (3) Outcomes: (i) efficacy end points: stroke or systemic embolism, myocardial infarction, and death from any cause; (ii) safety end points: major bleeding defined according to the 2005 International Society on Thrombosis and Hemostasis criteria[24] and clinically relevant nonmajor bleeding. Studies with insufficient data (not describe the data of NOACs, respectively), those not published in English, and certain publication types (eg, conference, abstracts, letters, comments, case reports, and reviews) were excluded from this NMA.

Literature Search

A comprehensive literature search of the PubMed, Elsevier, and Cochrane Library electronic databases was conducted by 2 independent reviewers (Qinmei Xiong and Cen Wang). The included studies were published from December 2010 to June 2019. Search terms included "atrial fibrillation," "NOACs," "dabigatran," "apixaban," "rivaroxaban," and "edoxaban." No research meeting the inclusion criteria was found in the manual search.

Data Extraction and Quality Assessment of Individual Studies

Data extraction was performed independently by 2 reviewers based on the inclusion and exclusion criteria. Initial screening was conducted by reading titles and abstracts of all studies. Full texts of selected research articles were then reviewed to confirm if those studies met the inclusion criteria. Additionally, disagreements were resolved through discussion or consultation with a third reviewer (Kui Hong).

Network Meta-Analysis and Statistical Analysis

Network meta-analysis was conducted to pool the results of direct and indirect comparisons using a Bayesian approach. All data were analyzed using STATA 15.0 and ADDIS (Aggregate Data Drug Information System) 1.16.8 software (Drug Information Systems, Groningen, the Netherlands). We first performed a pairwise meta-analysis to directly evaluate the treatment effect of NOACs. The odds ratio (OR) with a 95% confidence interval (CI) was applied to evaluate the end points. For the NMA, ORs with 95% credible intervals (CrIs) were used. Moreover, a consistency model based on the Markov chain Monte Carlo simulation method was applied by using 50 000 simulation iterations for each 4 chains with a burn-in period of the first 20 000 iterations. Node-splitting analysis and inconsistency standard deviation (ISD) were then performed to evaluate the consistency of the data. When the P value of the node-splitting analysis was >.05 and the 95% CI of the ISD contained 1, the consistency model was selected.[25] Convergence was evaluated using potential scale reduction factor (PSRF) and the Brooks-Gelman-Rubin method, and a value of ~ 1 represented good convergence. Value of $P < .05$ was regarded as a statistically significant result. We could also use the probabilities of treatment rankings to understand which interventions are more effective and safe; the total rank probability was 1. According to our pooled result, Rank 1 was the worst and Rank N was the best.

Results

Flow Diagram of Literature Search

Using the above-mentioned search strategies, we found a total of 1111 studies (743 in PubMed, 262 in Elsevier, 106 in Cochrane Library). We excluded 785 studies by reading the titles and abstracts. When we screened the full texts, 291 studies were eliminated because these studies did not relate to NOACs, Asian populations, and atrial fibrillation. Finally, 18 studies were included. The other studies were excluded for the following reasons: (1) certain publication types with no data (n = 7); (2) duplicate data without follow-up (n = 4); (3) studies not published in English (n = 3); and (4) studies not describing NOACs (apixaban, dabigatran, rivaroxaban, and edoxaban; n = 3; Figure 1).

Characteristics of the Included Studies and Patients

All 18 included studies were conducted in China,[12,13,15,18,26-28] Singapore,[12,15,19] Korea,[12-15,17-19,29] Japan,[12,13,15,30,31] India[12], Malaysia,[11,12,15,16,32] the Philippines,[12,15] Turkey,[33] Israel,[34] or Thailand.[12] A total of 71 227 anticoagulated patients with NVAF were studied. The oral anticoagulants were warfarin, apixaban, dabigatran, edoxaban, and rivaroxaban (Table 1).

Pairwise Meta-Analysis

The risk of stroke or systemic embolism was decreased by 60% and 55% for patients who took dabigatran and rivaroxaban, respectively, when compared to those who took warfarin (dabigatran vs warfarin [OR = 0.4; 95% CI: 0.26-0.6] and rivaroxaban vs warfarin [OR = 0.45; 95% CI: 0.28-0.72]). For death

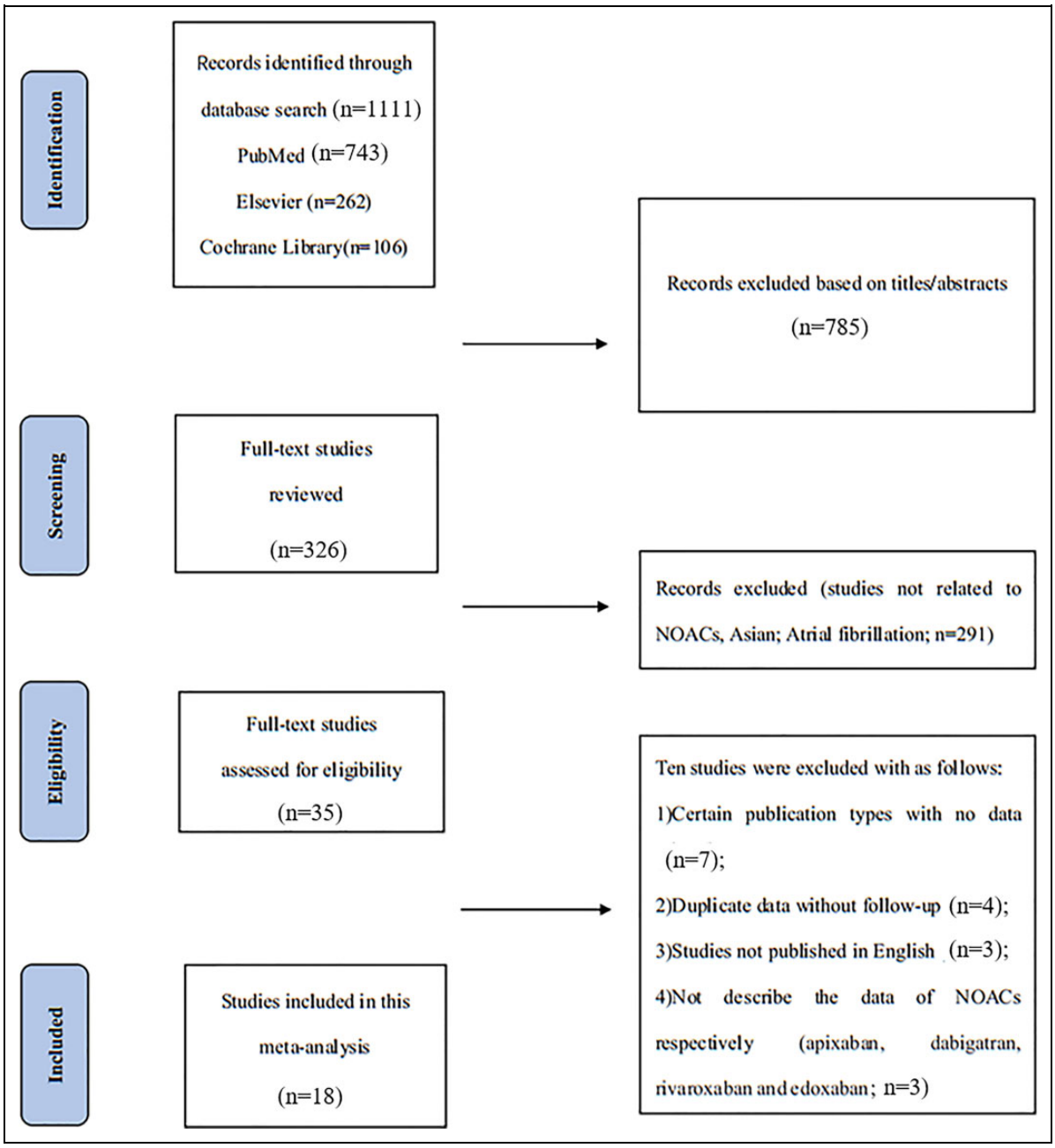

Figure 1. Flow diagram of literature search.

from any cause risk, the risk was decreased by 63% and 66% for patients who took rivaroxaban and dabigatran when compared to those who took warfarin (rivaroxaban vs warfarin: OR = 0.37; 95% CI: 0.21-0.67; dabigatran vs warfarin: OR = 0.34, 95% CI: 0.13-0.91). When compared to those who took warfarin, intracranial hemorrhage (ICH) was decreased by 81%, 67%, and 76% among patients who took apixaban, dabigatran, or rivaroxaban, respectively (apixaban vs warfarin: OR = 0.19, 95% CI: 0.05-0.72; dabigatran vs warfarin: OR = 0.33, 95% CI: 0.2-0.54; rivaroxaban vs warfarin: OR = 0.24, 95% CI: 0.18-0.33). No significant difference was found for myocardial infarction and major bleeding (Figure 2).

Network Meta-Analysis

In our NMA, the indirect comparisons of the NOACs were based on the published direct comparisons with the NOACs against warfarin. The data for this section were consistent with the pairwise meta-analysis. In node-splitting analysis, all of the *P* values were over .05, with the 95% CI of the ISD containing 1 and all of the PSRFs ranging from 1.00 to 1.01. This indicated that all included studies had good consistence, and the model obtained good convergence. Therefore, the consistency model was selected.

The indirect comparisons of all of the end points for the oral anticoagulants are shown in (Supplemental Table 1). There are

Table 1. Summary of Patients' Characteristics in 18 Included Studies.

Study	Country	Follow-Up, months	Study Arms	N	Drug	End Points
Chung et al (2011)[19]	Korea, Singapore	12	2	235	E/V	Major bleeding
Hori et al (2013)[12]	China, Japan, Korea, India, Malaysia, Philippines, Singapore, Thailand	24	2	2782	D/V	Stroke/SE; MI; Death; Major bleeding; ICH
Wong et al (2014)[18]	China, Korea	22	2	932	R/V	Stroke/SE; MI; Death; Major bleeding; ICH
Goto et al (2014)[15]	China, Japan, Korea, Philippines, Malaysia, Singapore	20	2	1993	A/V	Stroke/SE; MI; Death; Major bleeding; ICH
Yap et al (2016)[11]	Malaysia	20	2	1000	D/V	Stroke/SE; Major bleeding; ICH
Yamashita et al (2016)[13]	Japan, China, Korea	24	2	1943	E/V	Stroke/SE; MI; Death; Major bleeding; ICH
Cha et al (2017)[14]	Korea	24	4	34 833	A/D/R/V	Stroke/SE; Death; ICH
Lee et al (2017)[17]	Korea	24	2	1098	D/V	Stroke/SE; MI; Death; Major bleeding; ICH
Beshir et al (2018)[16]	Malaysia	12	3	1017	D/R/V	Major bleeding
Jeong et al (2019)[29]	South Korea	12	2	1608	R/V	Stroke/SE; MI; Death; Major bleeding; ICH
Mao et al (2014)[28]	China	18	2	353	R/V	Stroke/SE; major bleeding; ICH
Yamashita et al (2012)[31]	Japan	12	2	519	E/V	Major bleeding
Yap et al (2017)[32]	Malaysia	93	2	200	D/V	Stroke/SE; ICH
Naganuma et al (2017)[30]	Japan	10	2	362	D/V	Stroke/SE; Major bleeding
Li et al (2017)[26]	China	22	3	2099	D/R/V	Stroke/SE; ICH
Ho et al (2015)[27]	China	36	2	1821	D/V	Stroke/SE; Death; ICH
Yiginer et al (2016)[33]	Turkey	17	2	183	D/R	Death; Major bleeding; ICH
Ellis et al (2016)[34]	Israel	8	3	18 249	D/R/V	ICH

Abbreviations: SE, systemic embolism; MI, myocardial infarction; ICH, intracranial hemorrhage; V, vitamin-K antagonists (Warfarin); A, apixaban; D, dabigatran; R, rivaroxaban.

13 studies providing data on 15 direct comparisons between 4 different treatment nodes for major bleeding, 13 studies providing data on 20 direct comparisons between 4 different treatment nodes for stroke or systemic embolism, 13 studies providing data on 21 direct comparisons between 4 different treatment nodes for intracranial bleeding, 9 studies providing data on 14 direct comparisons between 4 different treatment nodes for death from any cause, and 6 studies providing data on 6 direct comparisons between 4 different treatment nodes for myocardial infarction (Figure 3). All the results of the NMA were consistent with the pairwise meta-analysis, but there were no significant differences among the NOACs in the 5 end points (Supplemental Table 1).

Although no significant differences were shown for all of the selected end points in the NMA, the rank probability of the 5 oral anticoagulants showed the degree of drug efficacy in each end point, which may provide guidance for medical decision-making in clinical practice. Apixaban likely has the most effective drug for the prevention of stroke or systemic embolism, death from any cause, major bleeding, and ICH, with rank probabilities of 0.47, 0.49, 0.42, and 0.51, respectively. For cases of myocardial infarction, rivaroxaban may be considered as the best drug, with ranking probabilities of 0.40 (Supplemental Figure 1).

Discussion

Our pairwise meta-analysis has demonstrated that dabigatran and rivaroxaban performed better than warfarin in cases of stroke or systemic embolism and death from any cause; apixaban, dabigatran, and rivaroxaban had a lower risk of ICH compared to warfarin. In our NMA, the ORs with 95% CrIs demonstrated no significant differences among the NOACs. Rank probability analysis showed that apixaban may have the highest efficacy for stroke or systemic embolism, death from any cause, major bleeding, and ICH; rivaroxaban may have the best performance for myocardial infarction. As far as we are aware, this is the first NMA comparing NOACs that is focused on Asian patients with NVAF.

The pairwise meta-analysis in Asians was generally consistent with previous studies. In the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, for example, dabigatran was superior to warfarin for stroke or systemic embolism, myocardial infarction, major bleeding, and intracranial bleeding.[7] 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 trial, rivaroxaban had a lower risk of ICH when compared to warfarin.[9] In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial, apixaban was superior to warfarin for stroke or systemic embolism, death from any cause, major bleeding, and intracranial bleeding.[6] In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation Thrombolysis in Myocardial Infarction 48 trial, edoxaban had a lower risk of death from any cause, major bleeding, and ICH when compared to warfarin.[8] Unfortunately, these 4 studies did not directly evaluate the differences in efficacy and safety comparing those NOACs to one another.

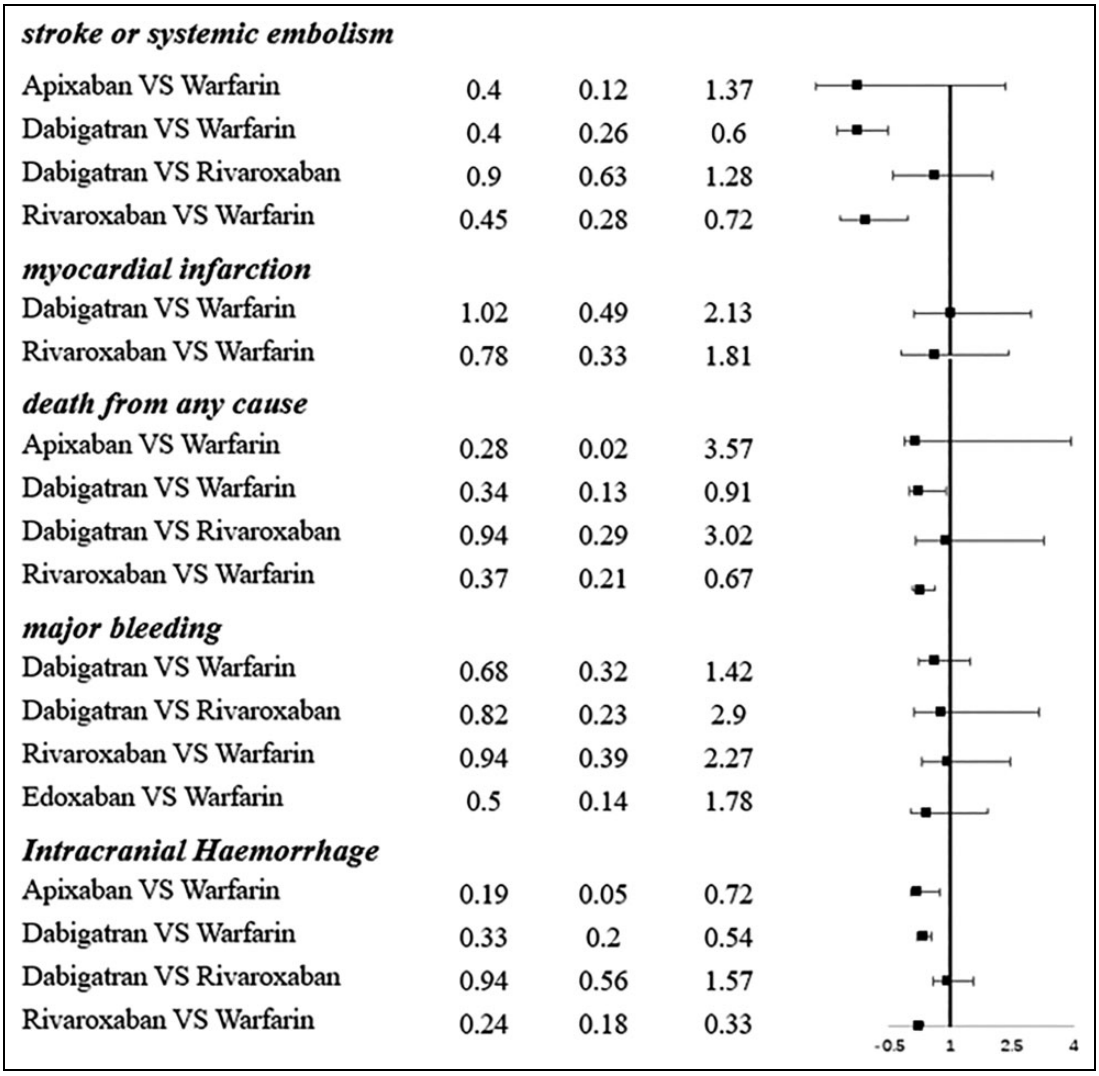

Figure 2. Pairwise meta-analysis results for 5 oral anticoagulants in 5 end points.

Cha et al[14] reported that rivaroxaban had a 1.94-fold elevated risk of stroke or systemic embolism when compared to apixaban (rivaroxaban vs apixaban: OR = 1.94; 95% CI: 1.01-3.71). In the death from any cause, dabigatran and rivaroxaban had a 2.22- and 3.83-fold elevated risk when compared to apixaban, respectively (dabigatran vs apixaban: OR = 2.22, 95% CI: 1.20-4.10; rivaroxaban vs apixaban: OR = 3.83, 95% CI: 2.16-6.79), and rivaroxaban has a 1.72-fold elevated risk when compared to dabigatran (rivaroxaban vs dabigatran: OR = 1.72, 95% CI: 1.24-2.40).

Body weight and BMI in Asians have been found to be lower than in white populations in many studies.[21,22] Low body weight ($\leq$60 kg) is an important covariate for bleeding, and Cha et al reported that being underweight increases the risk of major bleeding and all-cause death when compared to being normal weight or overweight.[14]

Indeed, Asians may have a propensity for bleeding events when taking warfarin.[12] For example, a previous study showed that Asian patients with AF treated with warfarin had a 4-fold higher hazard ratio (HR) for ICH when compared to whites.[22] In a recent meta-analysis, the incidence of ICH was approximately 2-fold higher in Asians compared to whites.[35] Additionally, the salt sensitivity of different ethnic groups may be related to ICHs.[36] Because more Asian patients with AF had ICH than did non-Asians, the developing countries appear to have 80% of the global burden of ICH.[37]

Several studies have demonstrated that patients with AF used NOACs to reduce the risk of bleeding.[38,39] In our pairwise meta-analysis, apixaban, dabigatran, and rivaroxaban had a lower risk than warfarin for ICH. In our NMA, the ORs with 95% CrIs demonstrated no significant differences among the NOACs, but the rank probability analysis showed that apixaban had the highest probability of performing the best among all anticoagulants for ICH.

Limitations

As an indirect comparison analysis, the present NMA has some inherent limitations. We found only 5 head-to-head studies on NOACs, and the 5 studies were conducted in China,[26]

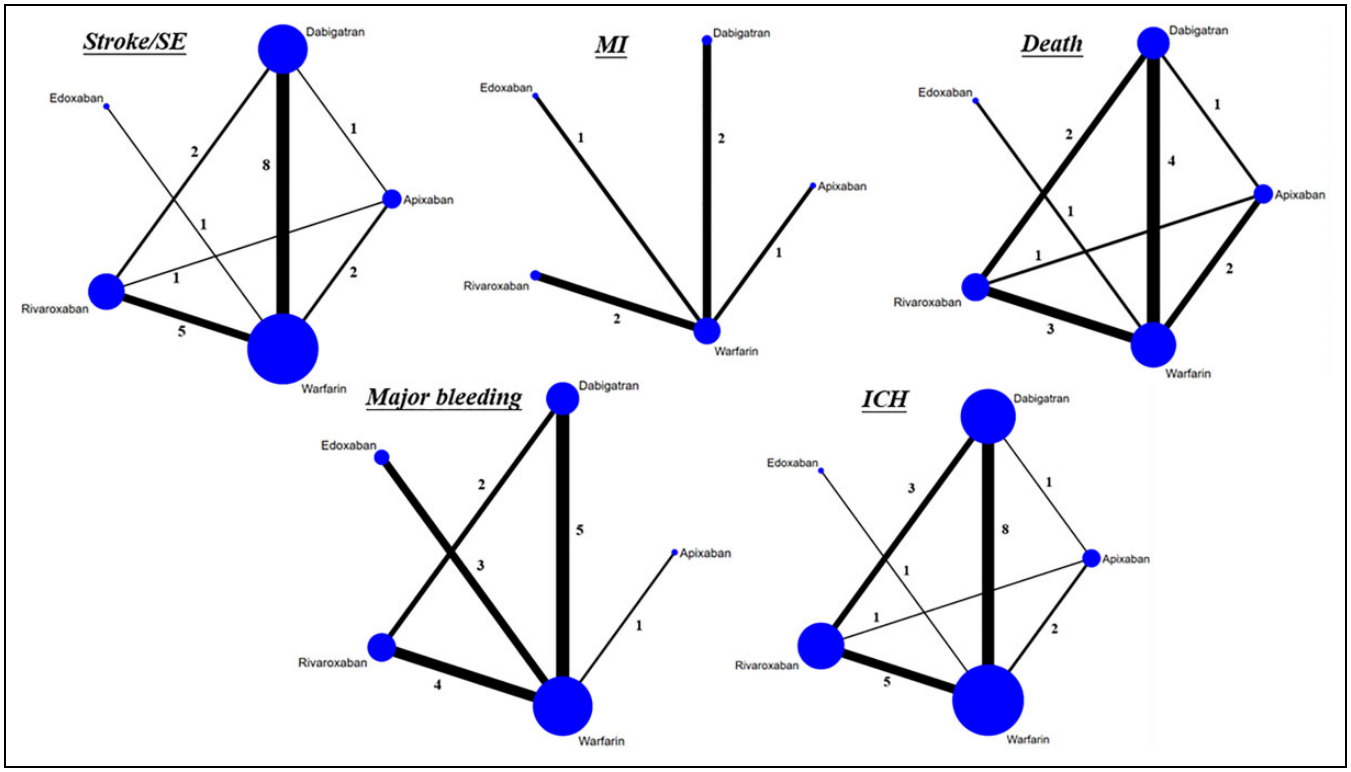

Figure 3. Network of the included comparisons.

Malaysia,[16] Israel,[34] and Korea.[14] More direct comparisons should be performed as the findings of indirect comparisons can only be considered as guidance for clinical practice. Moreover, heterogeneity for clinical, methodological, and statistical limitations always exists.

Conclusion

In our NMA, to indirectly compare the main efficacy and safety end points among NOACs in Asians with NVAF, there were no significant differences among the NOACs for efficacy, but rank probability analysis showed that apixaban probably performs best in stroke or systemic embolism, death from any cause, major bleeding, and ICH. For cases of myocardial infarction, rivaroxaban may be considered as the best drug.

Authors' Note

Gregory Y. H. Lip and Kui Hong are co-senior authors. Qinmei Xiong, Cen Wang, and Hualong Liu are co-first authors.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the National Natural Science Foundation of China [81530013 and 81600243] and Jiangxi Scientific Program [20151BBB70266 and 2016BAB215238]

ORCID iD

Kui Hong https://orcid.org/0000-0001-9416-0862

Supplemental Material

Supplemental material for this article is available online.

References

1. Albers GW, Dalen JE, Laupacis A Manning WJ, Petersen P, Singer DE. Antithrombotic therapy in atrial fibrillation. *Chest*. 2001;119(1 suppl):194S-206S.
2. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98(10): 946-952.
3. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23): 2071-2104.
4. Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur J Cardiothorac Surg*. 2016;50(5): e1-e88.
5. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857-867.

6. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011; 365(11):981-992.
7. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009; 361(12):1139-1151.
8. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013; 369(22):2093-2104.
9. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011; 365(10):883-891.
10. Huisman MV, Rothman KJ, Paquette M, et al. The changing landscape for stroke prevention in AF: findings from the GLORIA-AF Registry Phase 2. *J Am Coll Cardiol*. 2017;69(7): 777-785.
11. Yap LB, Eng DT, Sivalingam L, et al. A comparison of dabigatran with warfarin for stroke prevention in atrial fibrillation in an Asian population. *Clin Appl Thromb Hemost*. 2016;22(8): 792-797.
12. Hori M, Connolly SJ, Zhu J, et al. 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.
13. Yamashita T, Koretsune Y, Yang Y, et al. Edoxaban vs. warfarin in east Asian patients with atrial fibrillation—An ENGAGE AF-TIMI 48 subanalysis. *Circ J*. 2016;80(4): 860-869.
14. Cha MJ, Choi EK, Han KD, et al. Effectiveness and safety of non-vitamin K antagonist oral anticoagulants in Asian patients with atrial fibrillation. *Stroke*. 2017;48(11):3040-3048.
15. 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(3):303-309.
16. Beshir SA, Aziz Z, Yap LB, Chee KH, Lo YL. Evaluation of the predictive performance of bleeding risk scores in patients with non-valvular atrial fibrillation on oral anticoagulants. *J Clin Pharm Ther*. 2018;43(2):209-219.
17. Lee KH, Park HW, Lee N, et al. Optimal dose of dabigatran for the prevention of thromboembolism with minimal bleeding risk in Korean patients with atrial fibrillation. *Europace*. 2017;19(suppl_ 4):iv1-iv9.
18. Wong KS, Hu DY, Oomman A, et al. Rivaroxaban for stroke prevention in east Asian patients from the ROCKET AF trial. *Stroke*. 2014;45(6):1739-1747.
19. Chung N, Jeon HK, Lien LM, et al. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. *Thromb Haemost*. 2011;105(3):535-544.
20. Wang KL, Lip GY, Lin SJ, Chiang CE. Non-vitamin K antagonist oral anticoagulants for stroke prevention in Asian patients with nonvalvular atrial fibrillation: meta-analysis. *Stroke*. 2015;46(9): 2555-2561.
21. 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(3):210-219.
22. Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. *J Am Coll Cardiol*. 2007;50(4): 309-315.
23. Skjoth F, Larsen TB, Rasmussen LH, Lip GY. Efficacy and safety of edoxaban in comparison with dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation. an indirect comparison analysis. *Thromb Haemost*. 2014;111(5):981-988.
24. O'Brien EC, Simon DN, Thomas LE, et al. The ORBIT bleeding score: a simple bedside score to assess bleeding risk in atrial fibrillation. *Eur Heart J*. 2015;36(46):3258-3264.
25. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. *Stat Med*. 2010;29(7-8):932-944.
26. Li WH, Huang D, Chiang CE, et al. 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.
27. Ho CW, Ho MH, Chan PH, et al. Ischemic stroke and intracranial hemorrhage with aspirin, dabigatran, and warfarin: impact of quality of anticoagulation control. *Stroke*. 2015;46(1):23-30.
28. Mao L, Li C, Li T, Yuan K. Prevention of stroke and systemic embolism with rivaroxaban compared with warfarin in Chinese patients with atrial fibrillation. *Vascular*. 2014;22(4):252-258.
29. Jeong HK, Lee KH, Park HW, et al. 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.
30. 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. *J Arrhythm*. 2017;33(2):107-110.
31. Yamashita T, Koretsune Y, Yasaka M, et al. Randomized, multicenter, warfarin-controlled phase II study of edoxaban in Japanese patients with non-valvular atrial fibrillation. *Circ J*. 2012;76(8): 1840-1847.
32. Yap SH, Ng YP, Roslan A, et al. A comparison of dabigatran and warfarin for stroke prevention in elderly Asian population with nonvalvular atrial fibrillation: an audit of current practice in Malaysia. *Med J Malaysia*. 2017;72(6):360-364.
33. Yiginer O, Tezcan M, Tokatli A, Degirmencioglu G. Managing the treatment of the patients with stable angina like a chess player: making moves considering the next move of atherosclerosis. *J Geriatr Cardiol*. 2016;13(11):938-939.
34. Ellis MH, Neuman T, Bitterman H, et al. 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.
35. Van Asch CJ, Luitse MJ, Rinkel GJ, et al. Incidence, case fatality, and functional outcome of intracerebral haemorrhage over time, according to age, sex, and ethnic origin: a systematic review and meta-analysis. *Lancet Neurol*. 2010;9(2):167-176.

36. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ*. 2009;339:b4567.
37. Guo YT, Zhang Y, Shi XM, et al. Assessing bleeding risk in 4824 Asian patients with atrial fibrillation: The Beijing PLA Hospital Atrial Fibrillation Project. *Sci Rep*. 2016;6:31755. doi:10.1038/srep31755.
38. Hankey GJ, Stevens SR, Piccini JP, et al. Intracranial hemorrhage among patients with atrial fibrillation anticoagulated with warfarin or rivaroxaban: the rivaroxaban once daily, oral, direct factor Xa inhibition compared with vitamin K antagonism for prevention of stroke and embolism trial in atrial fibrillation. *Stroke*. 2014;45(5):1304-1312.
39. Chatterjee S, Sardar P, Biondi-Zoccai G, Kumbhani DJ. New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation. *JAMA Neurol*. 2013;70(12):1486-1490.