Systematic Review and Meta-Analysis

Medicine®

OPEN

Meta-analysis of the efficacy and safety of non-vitamin K antagonist oral anticoagulants with warfarin in Latin American patients with atrial fibrillation

Zhiyu Su, MS[a], Hao Zhang, MS[a], Wenfeng He, MD[b], Jianyong Ma, MD[c], Junquan Zeng, MS[d,*], Xinhua Jiang, MS[a,*]

Abstract

Background: Data of non-vitamin K antagonist oral anticoagulants (NOACs) in current management of atrial fibrillation (AF) are predominantly derived from North American and European regions. However, the effects of NOACs for stroke prevention in Latin America remain unclear. Therefore, we aimed to compare the efficacy and safety of NOACs with warfarin in Latin American patients with AF.

Methods: The PubMed and Embase databases were systematically searched until July 12, 2019 for applicable randomized clinical trials. The risk ratios (RRs) and 95% confidence intervals (CIs) were pooled using a random-effects model.

Results: Four trials involving 8943 Latin American patients were included in this meta-analysis. In anticoagulated patients with AF, Latin American patients had higher rates of stroke or systemic embolism and all-cause death compared with non-Latin American subjects. Compared with warfarin use, the use of NOACs was significantly associated with reduced risks of stroke or systemic embolism, major bleeding, intracranial bleeding, and any bleeding in Latin American patients. There were no significant differences in the risks of ischemic stroke, all-cause death, and gastrointestinal bleeding between Latin and non-Latin American groups. All the interactions between Latin and non-Latin American groups about efficacy and safety outcomes of NOACs compared with warfarin were non-significant (all $P_{interaction} > .05$).

Conclusions: Our meta-analysis suggested that the use of NOACs was at least non-inferior to warfarin use for stroke prevention in Latin American patients with AF.

Abbreviations: AF = atrial fibrillation, ARISTOTLE = apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation, CI = confidence interval, ENGAGE AF-TIMI 48 = effective anticoagulation with factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction 48, LatAm = Latin American, NOACs = non-vitamin K antagonist oral anticoagulants, RCTs = randomized clinical trials, RE-LY = randomized evaluation of long-term anticoagulation therapy, ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation, RR = risk ratio, SSE = stroke or systemic embolism, TTR = time within therapeutic range.

Keywords: anticoagulants, atrial fibrillation, Latin American, outcomes, warfarin

Editor: Leonardo Roever.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

HZ and WH are joint senior authors.

This study was supported by the National Natural Science Foundation of China [NO. 31960146], Provincial Natural Science Foundation of Jiangxi [NO. 20181BAB205024], and Scientific research project of education department of Hunan province [19C1152].

All authors declare that they have no potential conflicts of interest that might be relevant to the contents of this review.

Supplemental Digital Content is available for this article.

[a] Department of Cardiovascular Medicine, Xiangdong Hospital Hunan Normal University, Liling, Hunan, [b] Jiangxi Key Laboratory of Molecular Medicine, the Second Affiliated Hospital of Nanchang University, Nanchang, [c] Department of Pharmacology and Systems Physiology, University of Cincinnati College of Medicine, Cincinnati, Ohio, [d] Department of Internal Medicine, Jinggangshan University, Ji'an, Jiangxi, China.

[*] Correspondence: Junquan Zeng, Department of Internal Medicine, Jinggangshan University, Ji'an, Jiangxi, China (e-mail: commandozjq@tom.com); Xinhua Jiang, Department of Cardiovascular Medicine, Xiangdong Hospital Hunan normal University, Liling, Hunan, China (e-mail: xdysjxh@163.com).

How to cite this article: Su Z, Zhang H, He W, Ma J, Zeng J, Jiang X. Meta-analysis of the efficacy and safety of non-vitamin K antagonist oral anticoagulants with warfarin in Latin American patients with atrial fibrillation. Medicine 2020;99:18(e19542).

Received: 9 October 2019 / Received in final form: 11 February 2020 / Accepted: 12 February 2020

http://dx.doi.org/10.1097/MD.0000000000019542

1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia with a 5-fold increase in the risk of stroke. These high-risk AF patients should receive the appropriate anticoagulation therapy[1,2] including vitamin K antagonists (e.g., warfarin) and non-vitamin K antagonist oral anticoagulants (NOACs; i.e., dabigatran, rivaroxaban, apixaban, and edoxaban). Scientific evidences from large randomized clinical trials (RCTs) have demonstrated that the use of NOACs is superior or non-inferior to warfarin use in AF patients.[3–6] Potential advantages of NOACs mainly include better safety profiles, no need for routine anticoagulant monitoring, less drug–drug or drug–food interactions, and predictable pharmacokinetics. Current guidelines in AF recommend NOACs as alternatives to warfarin in the high-income regions.[7,8] However, several factors such as racial difference and high cost of NOACs should be assessed before recommendations in low- and middle- income countries from Latin America.

In 2010, the Global Burden of Disease Study has reported that the estimated AF prevalence in Latin America is higher than the global average.[9] In Latin America, AF prevalence will continue to rise because of an ageing population, along with poorly controlled risk factors of AF[10] (e.g., hypertension, heart failure, diabetes, obesity, and rheumatic valve disease). As such, AF-related stroke prevalence and its associated death increase dramatically. Anticoagulation therapy could reduce the burden of AF, and improve AF prognosis. The use of antithrombotic treatments such as warfarin and aspirin for AF stroke prevention in Latin America remains common. However, warfarin use will require the frequent anticoagulant monitoring, but there are no monitoring facilities in many parts of Latin America. Also, it is difficult to achieve an adequate control of international normalized ratio in warfarin users. In a post-hoc analysis of 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) trial, the median time within therapeutic range (TTR) achieved among AF patients treating with warfarin in Latin America is generally lower than that in Western guidelines (59% vs 70%).[11] Aspirin is no longer recommended for stroke prevention in current AF guidelines mainly because of an increased risk of bleeding. Moreover, many AF patients with a moderate-to-high risk of stroke in Latin America receive no anticoagulation therapy regardless of sex,[12,13] suggesting the need for improved management of AF in this region. In contrast, NOACs have a predictable pharmacokinetic profile, which may overcome many limitations associated with warfarin and aspirin use. However, the quantitative effects of NOACs with warfarin for AF stroke prevention in Latin America remain unclear.[14] In this meta-analysis, we aimed to compare the efficacy and safety of NOACs with warfarin in Latin American (LatAm) patients with AF.

2. Methods

The corresponding results of this meta-analysis were presented based on the Preferred Reporting Items for Reporting Systematic Reviews and Meta-analyses. The ethical approval was not provided because this study was performed by including the published studies. The data that support the findings of this meta-analysis will be available from the corresponding author on reasonable requests.

2.1. Search strategy

The PubMed and Embase databases were systematically searched until July 12, 2019 for all studies that comparing the effect of NOACs with warfarin in LatAm patients with AF. In the search, we included 3 categories of keywords using the Boolean operator "and": atrial fibrillation OR atrial flutter AND non-vitamin K antagonist oral anticoagulants OR direct oral anticoagulants OR dabigatran OR rivaroxaban OR apixaban OR edoxaban AND vitamin K antagonists OR warfarin. The detailed search strategy is shown in Supplemental Table 1, http://links.lww.com/MD/E85. In addition, we searched the reference lists of the included studies and review articles for additional reports.

2.2. Inclusion and exclusion criteria

Studies were included if they met the following criteria: study design: phase III RCTs, or sub-analyses of RCTs; interventions: NOACs (dabigatran, rivaroxaban, apixaban, or edoxaban) versus warfarin; study population: Latin American patients with nonvalvular AF; and outcomes: studies reported at least one of efficacy and safety outcomes. Efficacy outcomes included stroke or systemic embolism (SSE), ischemic stroke, and all-cause death; and safety outcomes included major bleeding, intracranial bleeding, gastrointestinal bleeding, and any bleeding. We excluded several study types with no relevant data such as reviews, case reports, case series, editorials, letters to editors, guidelines, or conference abstracts.

2.3. Objectives

The aims of this meta-analysis were to compare clinical outcomes between Latin and non-Latin American patients with NOACs or warfarin; and to compare efficacy and safety outcomes of NOACs versus warfarin stratified by region (i.e., Latin and non-Latin American) in AF patients.

2.4. Study selection and data extraction

All of the retrieved records were screened by 2 independent reviewers (ZS and HZ). According to the predefined criteria, we first read the titles and abstracts to screen out the potentially available studies, and then reviewed the full text of these studies in more detail. Any discrepancies were resolved by discussion with each other, or consultation with a third reviewer (JZ). For each included study, we collected the extracted the following information: study characteristics, patient demographics, type or dosage of NOACs, follow-up duration, and outcomes.

2.5. Risk of bias 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 domains including selection bias, selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases.[15,16] The bias risk of each study was scored as "low," "unclear," or "high" risk in each domain. In addition, a risk of bias assessment was also performed according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group.[17]

2.6. Statistical analysis

All of the statistical analyses were performed using the Review Manager 5.3 software (the Nordic Cochrane Center, Rigshospitalet, Denmark). The consistency tests were performed using the Cochrane Q test and I^2 statistic, where $P < .1$ and $I^2 > 50\%$ indicated a substantial heterogeneity, respectively. The risk ratios (RRs) and its corresponding 95% confidence intervals (CIs) were regarded as the effect estimates. The natural logarithms of RRs and its standard errors were calculated, and then pooled by a random-effects model using an inverse variance method. The sensitivity analysis or subgroup analysis was performed where appropriate. According to the Cochrane handbook, the publication bias was assessed via observing the symmetry characteristics in the funnel plots. A value of $P < .05$ was considered statistically significant.

3. Results

3.1. Study selection

The process of literature search is shown in Supplemental Figure 1, http://links.lww.com/MD/E84. A total of 19 records were identified via the electronic searches and the reference lists. Based on the title-/abstract- screenings, 10 studies were excluded because they were review articles or observational studies. And subsequently, 6 full-text studies[3–6,18,19] were reviewed in more detail, 2 of which were excluded because participants had a substantial overlap.[3,6] Finally, a total of 4 trials (2 phase III RCTs including ROCKET AF [rivaroxaban] and apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation [ARISTOTLE] [apixaban], 2 sub-analyses of RCTs including randomized evaluation of long-term anticoagulation therapy [RE-LY] [dabigatran], and effective anticoagulation with factor Xa next generation in atrial fibrillation-thrombolysis in myocardial infarction 48 [ENGAGE AF-TIMI 48] [edoxaban])[4,5,18,19] were included in this meta-analysis. The baseline characteristics of 4 included studies are shown in Supplemental Table 2, http://links.lww.com/MD/E85. The group of LatAm involved 5096 NOACs and 3867 warfarin users, while the group of non-LatAm included 37,265 NOACs and 25,362 warfarin users. Each of the included studies showed a low risk of bias (Supplemental Tables 3–4, http://links.lww.com/MD/E85).

3.2. Outcomes between LatAm and non-LatAm patients with anticoagulants

To compare the outcomes in anticoagulated patients with AF between LatAm and non-LatAm groups, we first performed meta-analyses separately for the NOACs and warfarin arms. As a result, there were no differences in the effect estimates between the NOACs and warfarin arms (all $P_{\text{interaction}} > .05$). Therefore, we then pooled the data of the NOACs and warfarin arms together.

Pooling data in Table 1 showed that the LatAm group had increased risks of SSE (RR = 1.15, 95% CI 1.01–1.30; Supplemental Figure 2, http://links.lww.com/MD/E84) and all-cause death (RR = 1.46, 95% CI 1.30–1.63; Fig. 1) as compared with the non-LatAm group. There were no significant differences in the rates of ischemic stroke (RR = 1.01, 95% CI 0.80–1.27; Supplemental Figure 3, http://links.lww.com/MD/E84), major bleeding (RR = 0.93, 95% CI 0.78–1.11; Supplemental Figure 4, http://links.lww.com/MD/E84), intracranial bleeding (RR = 1.42, 95% CI 0.96–2.08; Supplemental Figure 5, http://links.lww.com/MD/E84), gastrointestinal bleeding (RR = 1.03, 95% CI 0.80–1.34; Supplemental Figure 6, http://links.lww.com/MD/E84), and any bleeding (RR = 0.99, 95% CI 0.80–1.24; Supplemental Figure 7, http://links.lww.com/MD/E84).

3.3. Efficacy and safety of NOACs versus warfarin stratified by region

Because low-dose edoxaban (30 mg) has not been used in clinical practice, we performed the main analysis (Table 2) by excluding the low-dose edoxaban data[18] and then reperformed a more complete analysis by including the low-dose edoxaban data.[18]

3.3.1. Efficacy. NOACs significantly reduced the risk of SSE in LatAm (RR = 0.76, 95% CI 0.60–0.96) and non-LatAm patients (RR = 0.83, 95% CI 0.74–0.93) compared with warfarin ($P_{\text{interaction}} = .37$; Fig. 2). Pooling data showed a comparable risk of ischemic stroke in both LatAm and non-LatAm groups (Supplemental Figure 8, http://links.lww.com/MD/E84). Compared with warfarin use, the use of NOACs was associated with a decreased risk of all-cause death in non-LatAm patients (RR = 0.90, 95% CI 0.84–0.97) but not in LatAm (RR = 0.89, 95% CI 0.74–1.07) subjects ($P_{\text{interaction}} = .89$; Fig. 3).

3.3.2. Safety. Compared with warfarin use, the use of NOACs significantly decreased the risks of major bleeding (LatAm: RR =

Table 1

Outcomes in Latin American versus non-Latin American patients treating with anticoagulants.

	NOAC arm		Warfarin arm		Pooled treatment arms*	
	RR and 95%CI	*P* value	RR and 95%CI	*P* value	RR and 95%CI	*P* value
Efficacy outcomes						
SSE	1.15 (0.97–1.37)	.12	1.15 (0.95–1.38)	.14	1.15 (1.01–1.30)	.03
Ischemic stroke	1.04 (0.79–1.36)	.80	0.90 (0.51–1.57)	.70	1.01 (0.80–1.27)	.94
All-cause death	1.46 (1.27–1.68)	<.00001	1.45 (1.20–1.76)	.0001	1.46 (1.30–1.63)	<.00001
Safety outcomes						
Major bleeding	0.91 (0.77–1.07)	.25	0.95 (0.67–1.35)	.77	0.93 (0.78–1.11)	.93
Intracranial bleeding	0.99 (0.52–1.90)	.98	1.63 (0.87–3.06)	.13	1.42 (0.96–2.08)	.08
Gastrointestinal bleeding	1.20 (0.87–1.65)	.28	0.84 (0.58–1.22)	.36	1.03 (0.80–1.34)	.80
Any bleeding	0.97 (0.70–1.34)	.85	1.04 (0.70–1.53)	.86	0.99 (0.80–1.24)	.95

AF = atrial fibrillation, CI = confidence interval, NOACs = non-vitamin K antagonist oral anticoagulants, RR = risk ratio, SSE = stroke or systemic embolism.
* Pooled treatment arms = NOAC arm + warfarin arm.

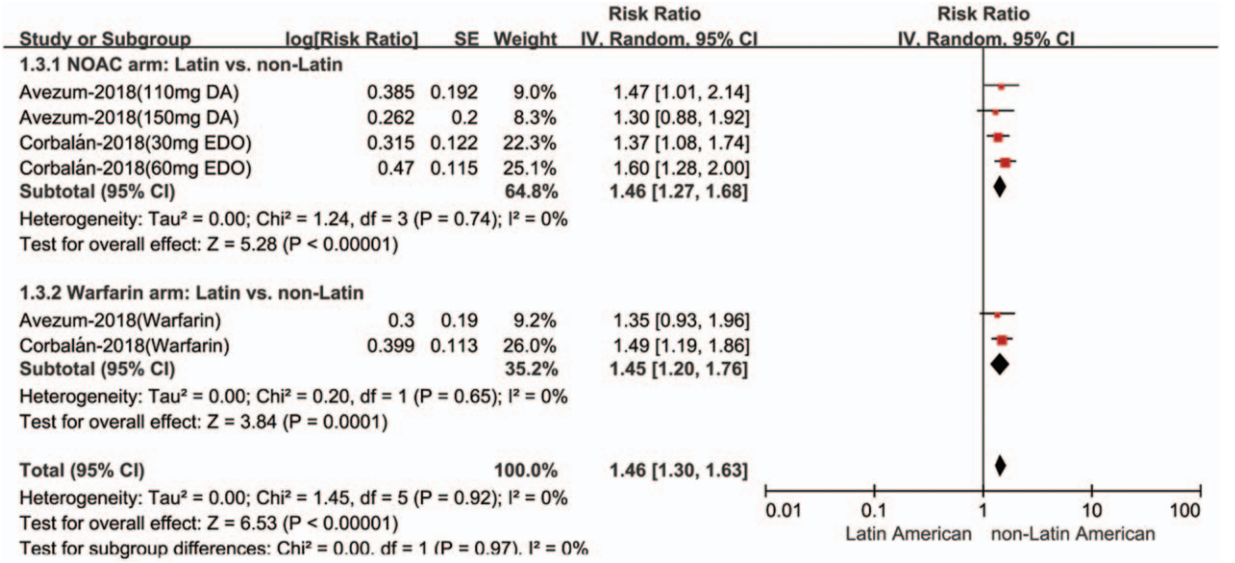

Figure 1. Forest plot of the outcome of all cause death by region (Latin vs non-Latin American) in AF patients. AF = atrial fibrillation, CI = confidence interval, DA = dabigatran, EDO = Edoxaban, IV = inverse of the variance, SE = standard error.

0.71, 95% CI 0.58–0.87; non-LatAm: RR = 0.81, 95% CI 0.74–0.89; Fig. 4), intracranial bleeding (LatAm: RR = 0.19, 95% CI 0.04–0.91; non-LatAm: RR = 0.42, 95% CI 0.31–0.57; Fig. 5), any bleeding (Supplemental Figure 9, http://links.lww.com/MD/E84) both in LatAm and non-LatAm patients (all $P_{\text{interaction}} > .05$). Pooling data with regard to gastrointestinal bleeding showed no significant interaction between LatAm and non-LatAm groups (Supplemental Figure 10, http://links.lww.com/MD/E84).

3.3.3. Sensitivity analysis. After exclusion of 1 study at a time, the corresponding RRs were not changed substantially. The results were also not changed when re-preforming the analysis using a fixed-effects model. A more complete analysis by adding the low-dose edoxaban data was presented in Supplemental Table 5, http://links.lww.com/MD/E85.

3.3.4. Subgroup analysis. Standard-dose NOACs included dabigatran 150 mg and edoxaban 60 mg, whereas low-dose NOACs included dabigatran 110 mg and edoxaban 30 mg. As shown in Supplemental Table 6, http://links.lww.com/MD/E85, standard-dose, but not low-dose NOACs significantly reduced the risk of SSE in LatAm patients. In addition, standard-dose NOACs had a strong trend toward a decrease in major bleeding, whereas low-dose NOACs significantly reduced this bleeding risk.

3.4. Publication bias

For the efficacy and safety outcomes, there were no significant publication biases by inspecting the funnel plots (Supplemental Figures 11–12, http://links.lww.com/MD/E84).

4. Discussion

In anticoagulated patients with AF, LatAm populations had increased rates of SSE and all-cause death compared with non-LatAm subjects. For the treatment effects, compared with warfarin use, the use of NOACs was associated with reduced risks of SSE, major bleeding, intracranial bleeding and any bleeding in LatAm patients. We observed no significant interactions between geographic regions with respect to efficacy and safety outcomes of NOACs compared with warfarin.

Table 2

Efficacy and safety outcomes between NOACs versus warfarin stratified by region.

	Latin American		Non-Latin American		
	RR and 95% CI	*P* value	RR and 95% CI	*P* value	*P*-interaction
Efficacy outcomes					
SSE	0.76 (0.60–0.96)	.02	0.83 (0.74–0.93)	.001	.51
Ischemic stroke	1.04 (0.67–1.62)	.86	0.94 (0.77–1.16)	.58	.70
All-cause death	0.89 (0.74–1.07)	.23	0.90 (0.84–0.97)	.005	.89
Safety outcomes					
Major bleeding	0.71 (0.58–0.87)	.001	0.81 (0.74–0.89)	<.0001	.27
Intracranial bleeding	0.19 (0.04–0.91)	.04	0.42 (0.31–0.57)	<.00001	.26
Gastrointestinal bleeding	1.34 (0.85–2.13)	.21	1.25 (1.07–1.46)	.005	.77
Any bleeding	0.74 (0.65–0.85)	<.0001	0.86 (0.79–0.93)	.0004	.08

AF = atrial fibrillation, CI = confidence interval, NOACs = non-vitamin K antagonist oral anticoagulants, RR = risk ratio, SSE = stroke or systemic embolism.

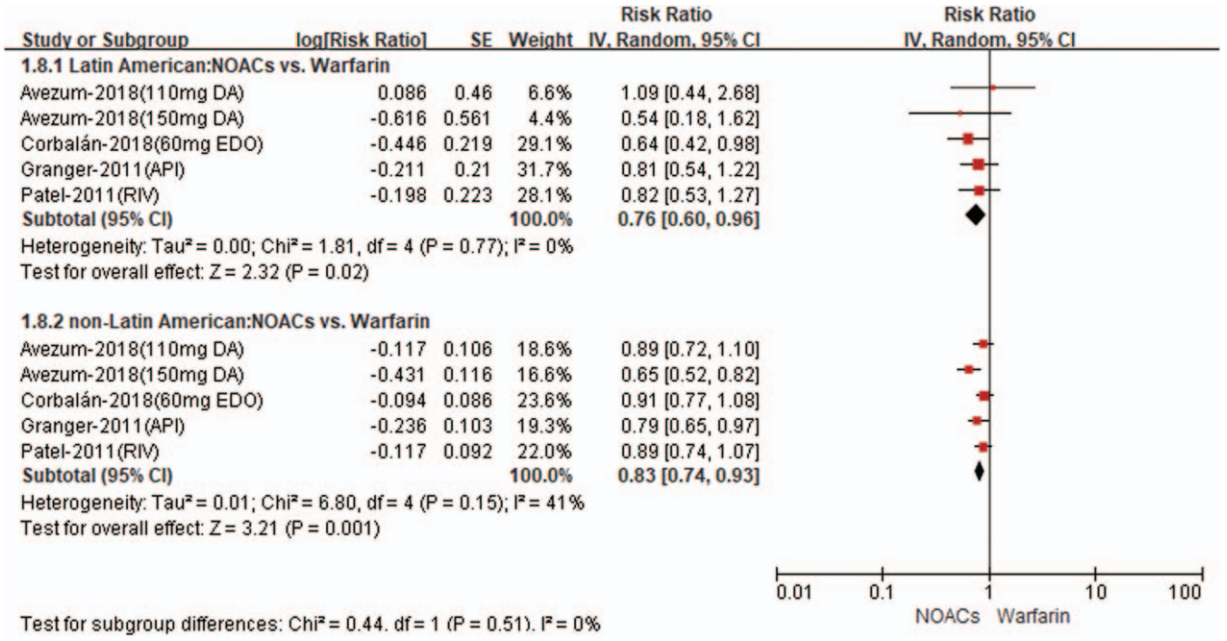

Figure 2. Forest plot of the outcome of SSE with NOACs versus warfarin stratified by region in AF patients. AF = atrial fibrillation, CI = confidence interval, DA = dabigatran, EDO = Edoxaban, IV = inverse of the variance, NOACs = non-vitamin K antagonist oral anticoagulants, SE = standard error.

The incidence of AF-related thromboembolic events is increasing in Latin America, possibly because of poorly controlled risk factors of AF.[14] Our current meta-analysis revealed a higher rate of all-cause death and a relatively weak association regarding SSE among LatAm subjects, suggesting the need for an adequate anticoagulation therapy of AF. The higher rate of death in LatAm patients persisted despite adjustment for baseline clinical characteristics.[18,20] The regional differences in patients' clinical characteristics may partially contribute to the higher rate of death in Latin America. For example, LatAm patients are less likely to be treated at baseline with evidence-based therapies such as beta-blockers and statins, but medications such as digitalis and amiodarone that are not associated with a reduction in death are administered more frequently.[18,21]

In Latin America, AF-related stroke prevalence and its associated death are increasing gradually, suggesting the need for appropriate stroke prophylaxis of AF. The variations in the baseline characteristics and antithrombotic treatment patterns for AF are remarkable in different LatAm countries.[22] Several major guidelines in Latin America including the Brazilian Society of Cardiology 2009,[23] the Brazilian Cardiogeriatrics Society,[24] and the Latin-American Society of Cerebrovascular Diseases[25] recommend the use of vitamin K antagonists for AF stroke

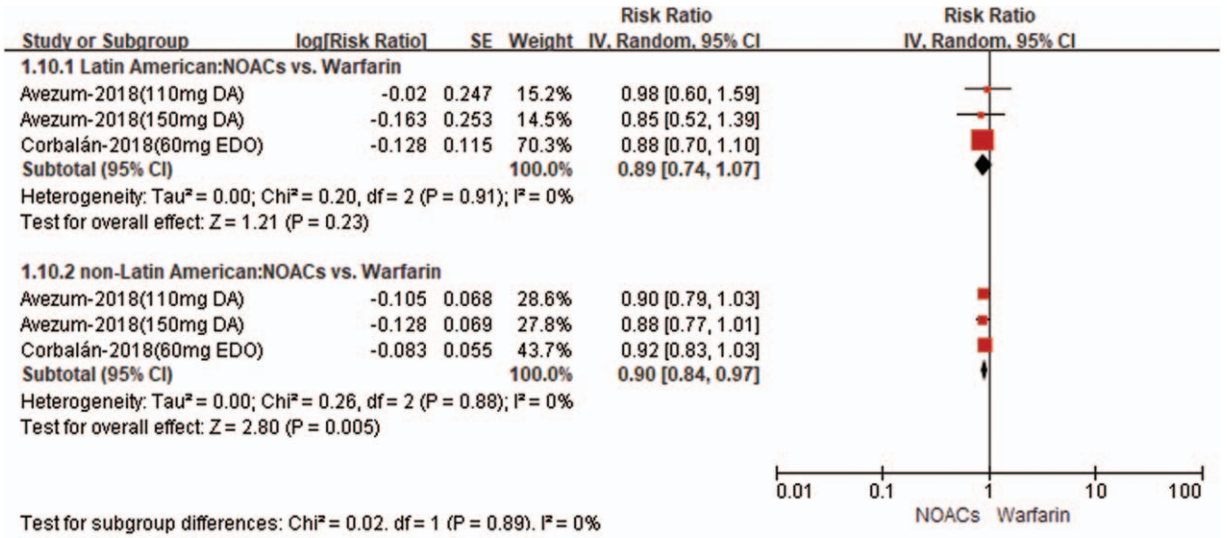

Figure 3. Forest plot of the outcome of all cause death with NOACs versus warfarin stratified by region in AF patients. AF = atrial fibrillation, CI = confidence interval, DA = dabigatran, EDO = Edoxaban, IV = inverse of the variance, NOACs = non-vitamin K antagonist oral anticoagulants, SE = standard error.

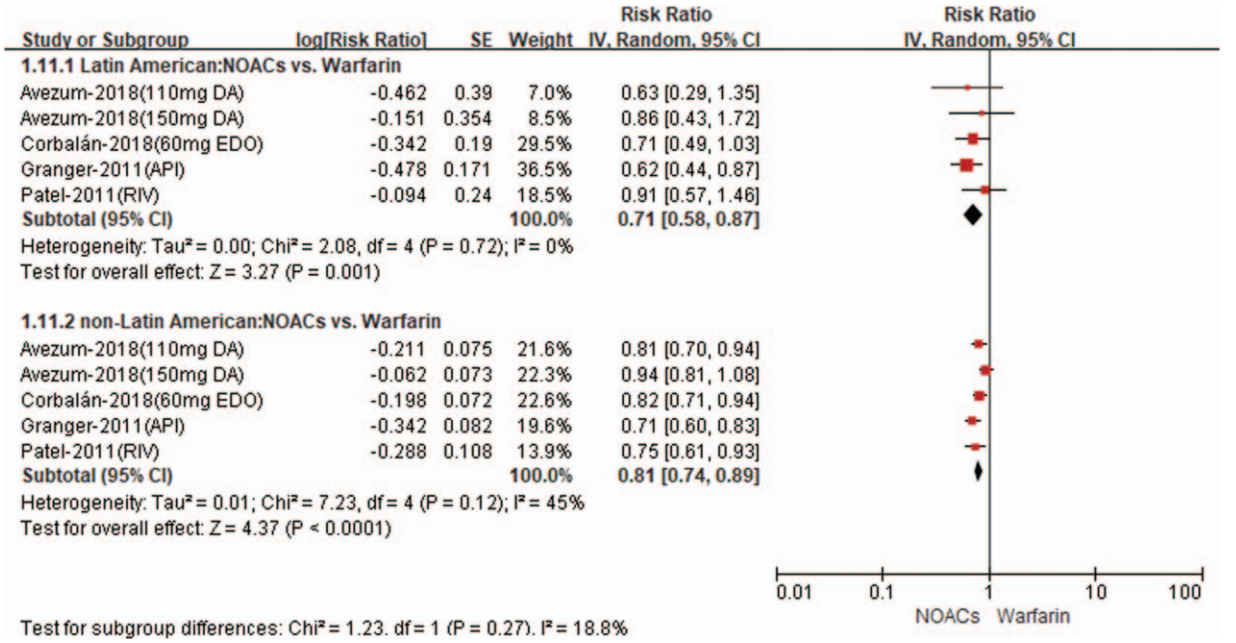

Figure 4. Forest plot of the outcome of major bleeding with NOACs versus warfarin stratified by region in AF patients. AF = atrial fibrillation, CI = confidence interval, DA = dabigatran, EDO = Edoxaban, IV = inverse of the variance, NOACs = non-vitamin K antagonist oral anticoagulants, SE = standard error.

prevention. However, there is a significant proportion of high-risk patients receiving no anticoagulation. Nearly 46% of outpatients do not receive anticoagulation according to the guidelines, ranging from 41.8% in Brazil to 54.8% in Colombia.[26] In addition, there is still a high use of aspirin as an alternation to anticoagulation for AF stroke prevention.

4.1. Comparing with previous studies and implications

Anticoagulation therapy in LatAm patients with AF mainly rely on the use of warfarin and aspirin, which have substantial limitations such as the need for monitoring and the increased bleeding risks. As such, the use of NOACs may be a better option for reducing the risk of AF-related stroke in LatAm patients. Previous studies on cost-effectiveness comparisons with warfarin have suggested that the use of NOACs in AF patients with moderate to severe risk of stroke is cost-effective.[27,28] Increasing the access to NOACs such as rivaroxaban could help improve the cost allocation.[29] To our knowledge, we first conducted a meta-analysis of 4 RCTs to determine the efficacy and safety of NOACs with warfarin in LatAm patients with AF. We found that NOACs reduced the risks of SSE and major bleeding in LatAm patients, suggesting the potential benefits of NOACs in these populations. The model estimations using epidemiological data in Argentina

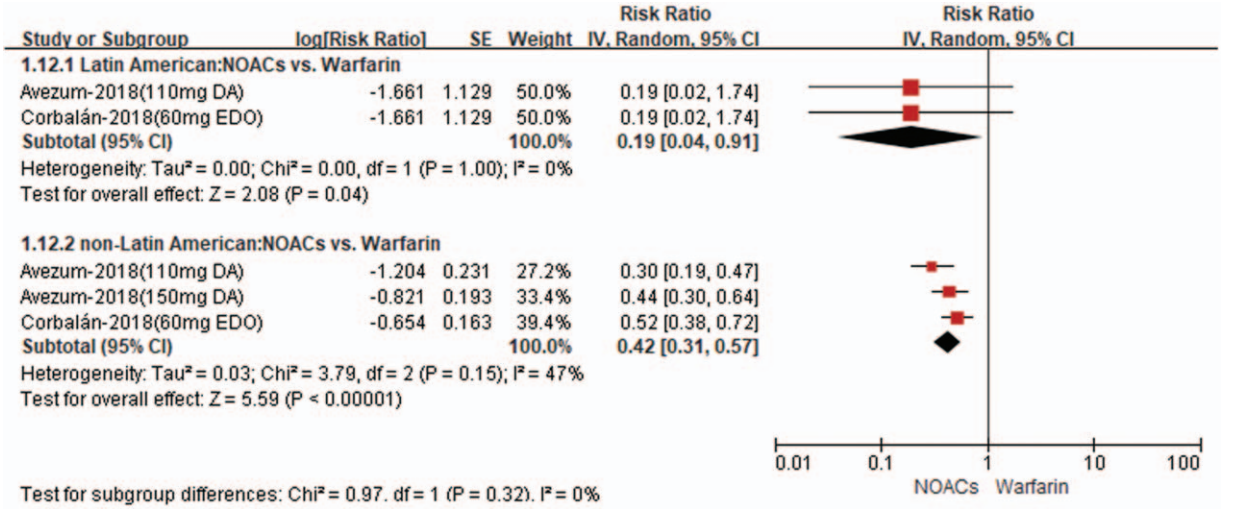

Figure 5. Forest plot of the outcome of intracranial bleeding with NOACs versus warfarin stratified by region in AF patients. AF = atrial fibrillation, CI = confidence interval, DA = dabigatran, EDO = Edoxaban, IV = inverse of the variance, NOACs = non-vitamin K antagonist oral anticoagulants, SE = standard error.

also suggested that apixaban relative to warfarin in AF patients could reduce the disease burden and costs, and improve patients' survival and quality of life.[30] In Eastern Europe, the Middle East, Africa and Latin America, XANTUS-EL study confirmed low stroke and bleeding risks in AF patients treated with rivaroxaban[31];however, warfarin was not the reference in this study. To date, there are still no observational studies directly focusing on the effect of NOACs versus warfarin in LatAm patients with AF.

The GLORIA-AF Phase II Registry has demonstrated substantial interregional and intraregional differences in antithrombotic treatments for AF.[32] Our meta-analysis could add contemporary data on clinical characteristics, management and outcomes of LatAm patients, suggesting the consistency of effects regardless of geographical regions, and more favorable efficacy and safety profiles in patients treated with NOACs. Consistent with the previous data,[4,5,18,19] we indicated that the use of NOACs were at least non-inferior to warfarin for stroke prevention in LatAm patients with AF. Our current meta-analysis provided an important contemporary picture of the response to anticoagulation therapy for LatAm patients; and might provide encouragement to select the use of NOACs for reducing AF-related stroke and death in LatAm patients.[33]

4.2. Limitations

Several limitations should be acknowledged in this meta-analysis. First, the numbers of included studies in some comparisons were relatively small, limiting the validity of these findings. For example, only 2 studies were included in the subgroup analysis based on the NOAC dosing; and thus, our data in relation to different doses of NOACs versus warfarin should be interpreted cautiously. Second, we did not perform the subgroup analysis based on TTR of warfarin users because of a limited number of studies. Third, the adherence or persistence to NOACs were not considered, which could affect the efficacy and safety outcomes. Finally, since the individual patient-level data could not be acquired from the included studies, some of the patients enrolled in LatAm regions in these studies might not be ethnically LatAm.

4.3. Future directions

The drawback of our meta-analysis lies on the design of the included studies, being the post-hoc, not pre-specified analysis of randomized prospective data. As such, there may be lack of statistical power to reliably detect the differences in the efficacy and safety outcomes between NOACs versus warfarin among LatAm patients with AF. In addition, patients from RCTs are generally selected with strict eligibility criteria, which are not always valid for patients in the real-world settings. Therefore, further observational cohort studies should confirm our findings based on the data of RCTs.

5. Conclusions

Based on published data, our meta-analysis suggested that the use of NOACs was at least non-inferior to warfarin use for stroke prevention in LatAm patients with AF.

Author contributions

Data curation: Zhiyu Su, Wenfeng He, Hao Zhang.
Formal analysis: Hao Zhang, Zhiyu Su.
Investigation: Zhiyu Su.
Methodology: Wenfeng He, Zhiyu Su.
Software: Wenfeng He, Hao Zhang, Zhiyu Su.
Supervision: Xinhua Jiang
Validation: Wenfeng He, Wengen Zhu.
Writing – original draft: Zhiyu Su, Jianyong Ma.
Writing – review & editing: Junquan Zeng, Xinhua Jiang.
junquan zeng orcid: 0000-0001-9823-8284.

References

[1] Zhu W, Xiong Q, Hong K. Meta-analysis of CHADS2 versus CHA2DS2-VASc for predicting stroke and thromboembolism in atrial fibrillation patients independent of anticoagulation. Tex Heart Inst J 2015;42:6–15.
[2] Zhu W, Fu L, Ding Y, et al. Meta-analysis of ATRIA versus CHA2DS2-VASc for predicting stroke and thromboembolism in patients with atrial fibrillation. Int J Cardiol 2017;227:436–42.
[3] Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus Warfarin in patients with atrial fibrillation. New Engl J Med 2013;369:2093–104.
[4] Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. New Engl J Med 2011;365:981–92.
[5] Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. New Engl J Med 2011;365:883–91.
[6] Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. New Engl J Med 2009;361:1139–51.
[7] January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration With the Society of Thoracic Surgeons. Circulation 2019;140:R665.
[8] Kirchhof P, Benussi S, Kotecha D, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J 2016;37:2893–962.
[9] Chugh SS, Havmoeller R, Narayanan K, et al. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. Circulation 2014;129:837–47.
[10] Cubillos L, Haddad A, Kuznik A, et al. Burden of disease from atrial fibrillation in adults from seven countries in Latin America. Int J Gen Med 2014;7:441–8.
[11] Singer DE, Hellkamp AS, Piccini JP, et al. Impact of global geographic region on time in therapeutic range on warfarin anticoagulant therapy: data from the ROCKET AF clinical trial. J Am Heart Assoc 2013;2: e000067.
[12] Jerjes Sanchez C, Corbalan R, Barretto ACP, et al. Stroke prevention in patients from Latin American countries with non-valvular atrial fibrillation: insights from the GARFIELD-AF registry. Clin Cardiol 2019;42:553–60.
[13] Antonio GJ, Baños-González MA, Guevara-Valdivia ME, et al. Gender differences and management of stroke risk of nonvalvular atrial fibrillation in an upper middle-income country: insights from the CARMEN-AF registry. Int J Cardiol Heart Vasc 2019;22:117–22.
[14] Massaro AR, Lip G. Stroke prevention in atrial fibrillation: focus on Latin America. Arq Bras Cardiol 2016;107:576–89.
[15] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
[16] Fu L, Zhu W, Huang L, et al. Efficacy and safety of the use of non-vitamin k antagonist oral anticoagulants in patients with ischemic heart disease: a meta-analysis of phase III randomized trials. Am J Cardiovasc Drug 2019;19:37–47.
[17] Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence–study limitations (risk of bias). J Clin Epidemiol 2011;64:407–15.
[18] Corbalán R, Nicolau JC, López-Sendon J, et al. Edoxaban versus warfarin in Latin American patients with atrial fibrillation. J AM Coll Cardiol 2018;72:1466–75.
[19] Avezum A, Oliveira GBDF, Diaz R, et al. Efficacy and safety of dabigatran versus warfarin from the RE-LY trial. Open Heart 2018;5: e800.

[20] Corbalan R, Hellkamp AS, Becker RC, et al. Latin American patients with AF have a higher risk profile but similar response to rivaroxaban versus warfarin (abstr). Circulation 2017;136(suppl):A17226.
[21] Silva H, Hernandez-Hernandez R, Vinueza R, et al. Cardiovascular risk awareness, treatment, and control in urban Latin America. Am J Ther 2010;17:159–66.
[22] Jerjes-Sanchez C, Corbalan R, Barretto A, et al. Stroke prevention in patients from Latin American countries with non-valvular atrial fibrillation: insights from the GARFIELD-AF registry. Clin Cardiol 2019;42:553–60.
[23] Lanas F, Castro C, Vallejos C, et al. Latin American clinical epidemiology network series – Paper 2: Apixaban was cost-effective vs. acenocoumarol in patients with nonvalvular atrial fibrillation with moderate to severe risk of embolism in Chile. J Clin Epidemiol 2017;86:75–83.
[24] Cantú-Brito C, Silva GS, Ameriso SF. Use of guidelines for reducing stroke risk in patients with nonvalvular atrial fibrillation: a review from a Latin American Perspective. Clin Appl Thromb Hemost 2018;24:22–32.
[25] Alonso DLM, Perez-RGE, Diez-Tejedor E. [Recommendations for stroke treatment and prevention, 2004]. Rev Neurol 2004;39: 465–86.
[26] Stambler B, Scazzuso F. Targeting stroke risk and improving outcomes in patients with atrial fibrillation in Latin America. Sao Paulo Med J 2016;134:534–42.
[27] Lanas F, Castro C, Vallejos C, et al. Latin American clinical epidemiology network series - paper 2: apixaban was cost-effective vs. acenocoumarol in patients with nonvalvular atrial fibrillation with moderate to severe risk of embolism in Chile. J Clin Epidemiol 2017;86:75–83.
[28] Cantú-Brito C, Silva GS, Ameriso SF. Use of guidelines for reducing stroke risk in patients with nonvalvular atrial fibrillation: a review from a Latin American Perspective. Clin Appl Thromb Hemost 2016;24:22–32.
[29] Soriano MA, Leyva-Bravo V, González-Rojas GL, et al. Treatment costs of ischemic stroke prevention and management in patients with Atrial Fibrillation (AF) in Latin America: Argentina, Brazil, Chile, and Venezuela. Value Health 2013;16:A705.
[30] Giorgi MA, Caroli C, Moore P, et al. Estimation of the effectiveness of apixaban in non valvular atrial fibrillation in anticoagulant suitable population in Agrentina. Eur Heart J 2013;34:3351.
[31] Martínez CAA, Lanas F, Radaideh G, et al. XANTUS-EL: A real-world, prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation in Eastern Europe, Middle East, Africa and Latin America. Egypt Heart J 2018;70:307–13.
[32] Mazurek M, Huisman MV, Rothman KJ, et al. Regional differences in antithrombotic treatment for atrial fibrillation: insights from the GLORIA-AF Phase II Registry. Thromb Haemost 2017;117:2376–88.
[33] Dubner SJ, Martinenghi N. Edoxaban in Latin America. J Am Coll Cardiol 2018;72:1476–7.