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

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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\textsubscript{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
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 Latin American 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 I² 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[3,6,16,18,19] 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] [darbixatran], 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 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 $P_{interaction}>.05$). 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 ($P_{interaction} = .37$; 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 ($P_{interaction} = .89$; 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 |
|-----------------|-----------------|-----------------|-----------------|
| | 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) | <.0001 | 1.45 (1.20–1.76) | .0001 | 1.46 (1.30–1.65) | <.0001 |
| **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) | 0.98 | 1.63 (0.37–3.06) | .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) | .96 |

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.
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 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 150mg and edoxaban 60mg, whereas low-dose NOACs included dabigatran 110mg and edoxaban 30mg. 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 | 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.
The incidence of AF-related thromboembolic events is increasing in Latin America, possibly because of poorly controlled risk factors of AF.\cite{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.\cite{18,20,21} 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.\cite{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.\cite{22} Several major guidelines in Latin America including the Brazilian Society of Cardiology 2009,\cite{23} the Brazilian Cardiogeriatrics Society,\cite{24} and the Latin-American Society of Cerebrovascular Diseases\cite{25} recommend the use of vitamin K antagonists for AF stroke

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**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.

**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.
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
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.[10] 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;[33] 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 based on TTR of warfarin users because of a limited number of studies. 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

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