Anticoagulant and Antiplatelet therapy for the prevention of stroke in AF with arterial origin stroke: a meta-analysis.

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Research article

Keywords: stroke, anticoagulant, antiplatelet, arterial origin, atrial fibrillation, meta- analysis

Posted Date: December 13th, 2019

DOI: https://doi.org/10.21203/rs.2.18775/v1

Abstract

Background Anticoagulation and antiplatelet therapy were adopted respectively for the prevention ofcardio-embolic stroke or arterial origin stroke. while it's difficult to make decisions for individual with Atrial fibrillation(AF)and arterial origin stroke as comorbidities, so we attempted to evaluate the efficacy and safety ofanticoagulants and antiplatelet forthe prevention of stroke in AF with arterial origin stroke and make an optimal treatment for these comorbidities.

Methods Databases included PubMed, Cochrane Library and ClinicalTrials.gov were searched up to 31 Aug 2019. Eight RCTs with 77048 participants were enrolled.

Results Direct oral anticoagulants(DOACs) reduced the relative risk of stroke and systemic embolism by 15% (95%CI 0.75-0.97, I2=65.6%) and the major bleeding by 23%(95%CI 0.63-0.95, I2=92.3%,). DOACs or warfarin plus aspirin compared with DOACs or warfarin alone did not show the benefit on stroke and systemic embolism prevent in AF patients, but increase the risk of major bleeding with RR 1.40 (95%CI 1.13-1.75,) and 1.33（95%CI 1.09-1.63）respectively. No differences in preventionof ischemic stroke were detected between OACs versus aspirin in arterial origin stroke. The major bleeding was significantly higher in the OACs group (RR,2.40,1.46-3.94, I2=62.2%). However, compared with aspirin, rivaroxabandid not increase the risk of major bleeding in Branch atheromatous stroke (RR,1.54,95%CI 0.26-9.12).

Conclusions We speculatedthat DOACs alone may be enough to prevent stroke recurrence and not to increase the risk of bleeding in AF patients with arterial origin stroke. The well designed RCTs with the direct comparison would be needed in future.

Background

Atrial fibrillation(AF) was a major risk factor for ischemic stroke. The Framingham study indicated that valvular AF increased the risk of ischemic stroke 17-fold and non-valvular AF(NVAF) increased the risk 5-fold.[1] Oral Anticoagulants (OACs) played a pivotal role in preventing cardio-embolic stroke. While it remained difficult to make decisions for individual in clinical practice, because the common comorbidities including peripheral artery disease or carotid disease or coronary artery disease were presented in AF patients who required not only OACs but antiplatelet therapy.[2] Especially, Atherosclerotic intracranial and extracranial arterial stenosis and other arterial origin stroke are another important causes of stroke, the guideline recommended antiplatelet therapy as a long term secondary prevention of ischemic stroke.[3] When Atherosclerotic and AF as comorbidities presented in same patient, what's the optimal treatment for antithrombotic therapy? How to balance the serious risk of ischemic stroke against that of major bleeding?

Warfarin and Direct Oral Anticoagulants (DOACs) were common OACs. Recent randomized trials have shown that DOACs were noninferior to warfarin in preventing stroke or systemic embolism, but less frequently intracranial and fatal bleeding in AF patients.[4–7] Warfarin was associated with significantly higher rates of adverse events and no benefit over aspirin in stroke with atherosclerotic arterial stenosis.[8–10] OACs plus antiplatelet therapy were recommended to use in AF patients with percutaneous coronary intervention(PCI).[11] While WAVE study showed the combination of an OAC with antiplatelet therapy was

not more effective than antiplatelet therapy alone in preventing major cardiovascular complications but increased the life-threatening bleeding in peripheral arterial disease.[12] The COMPASS trial[13] indicated that the combination of rivaroxaban 2.5 mg twice daily and aspirin in stable peripheral or carotid artery disease reduced major adverse cardiovascular. The combination may provide a protocol in AF patients with atherosclerotic disease as comorbidities. However, rivaroxaban doses used were lower compared with that used for stroke prevention in AF, and very few AF patients were included.

NO RCTs directly evaluated the efficacy and safety of anticoagulants versus antiplatelet therapy for the prevention of stroke in atrial fibrillation with arterial origin stroke. So in this meta-analysis, we attempted to indirectly demonstrate optimal treatment with two-step in atrial fibrillation with arterial origin stroke. Firstly, to assess the efficacy and safety of OACs plus antiplatelet versus OACs for the prevention of stroke in NVAF. Secondly, to assess the efficacy and safety of OACs versus antiplatelet therapy in stroke of arterial origin. And finally, we attempted to make an optimal treatment for the prevention of stroke in atrial fibrillation with arterial origin stroke.

Methods

The meta-analysis was performed according to the criteria reported by the PRISMA group.

Search strategy

Databases included PubMed, Cochrane Library and ClinicalTrials.gov with search keywords ‘antiplatelet therapy’, 'aspirin‘, ‘clopidogrel’, ‘oral ‘anticoagulants ‘, ‘warfarin’, ‘rivaroxaban’, ‘edoxaban’, ‘apixaban’, ‘dabigatran ‘,’cerebral ischemia’, ‘cerebral infarction’, ‘arterial Stenosis’, ‘arterial origin’, ‘atherosclerotic’ and ‘randomized controlled trial’ up to June 2019. The existing reviews of antithrombotic therapy in AF and arterial stenosis were also searched. The search was restricted to English language and published articles.

Study selection

Three authors (ZXL, TYB, LH) independently screened the search results, excluded irrelevant publications based on the title and abstract, and then obtained full texts of potentially relevant articles. The other three authors (YQR,ZY,LJJ) selected eligible studies according to the following criteria: (1) only randomized controlled trials were included, (2) OACs versus Antiplatelet or DOACs versus Warfarin with or without antiplatelet were assessed; (3) the efficacy outcomes and the safety outcomes were reported.In addition, trials were excluded based on the following criteria: (1) those with short follow-up(less than 3 months) and small sample(less than 100); (2) published only as abstracts; (3) those without standard adjusted dose warfarin (INR 2–3);(4) patients with percutaneous coronary intervention in three month

Data extraction

Two neurologists (LMX, SJK) independently extracted the following information: data on trial design, blinding, mean age, female No., study country, size of the sample, type of quality event, duration of follow-

up and the number of the lost, all primary efficacy and safety events. The scale of Jadad was used for quality assessment. Score 3–5 was assessed as high quality and score 0–2 was assessed as low quality.

Outcomes

The prespecified primary efficacy outcomes were the composite of stroke and systemic embolism in AF patients, and ischemic stroke in arterial origin stroke. The prespecified primary safety outcome was major bleeding. Each outcome was assessed according to the definitions reported in the original study protocols.

Statistical Analysis

Results of relative risks (RRs) for categorical variables (dichotomous outcomes) with 95% confidence intervals (CIs) were adopted to assess the efficacy and safety. Significance was set at $P < 0.05$. Intention-to-treat analysis was adopted. The presence of heterogeneity was quantified by the chi-squared test and I2 with significance being set at $P < 0.10$ statistically. The fixed-effect model was used to assess low heterogeneity ($I2 < 50\%$ or $P < 0.10$), and the random-effect model was used to assess high heterogeneity. Publication bias was assessed for the primary efficacy and safety end points using funnel plots. The linear regression method was used to detect funnel plot asymmetry. The subgroup was also performed on comparison of different medicine. Stata SE(version14.1) was used to perform this meta-analysis.

Results

A total of 8 RCTs were identified and included in this analysis with a total of 77048 participants enrolled. 4 for AF and 4 for arterial origin stroke. Figure 1 showed the flowchart of the study selection process. The mean age of patients was 67 years, and the mean follow-up ranged from 11 months to 4.6 years. Detailed baseline characteristics of included patients were listed in table1.

Compared with warfarin in AF patients, DOACs reduced the risk of stroke and systemic embolism by 15% (95%CI 0.75–0.97, $I^2 = 65.6\%$, $p = 0.012$) (Figure 2), and did not increase the risk of major bleeding. Conversely, the relative risk of major bleeding was reduced by 23%(95%CI 0.63–0.95, $I^2 = 92.3\%$, p□0.001) (Figure 3). The higher dosage of dabigatran showed a significantly lower risk of the primary efficacy outcome and this reduction did not make for a higher risk of major bleeding (RR, 0.94; 95% CI, 0.82–1.07).

The subgroup analysis indicated that DOACs plus aspirin or warfarin plus aspirin compared with DOACs or warfarin alone did not show the benefit on stroke and systemic embolism prevent in AF patients, but increase the risk of major bleeding with RR 1.40 (95%CI 1.13–1.75,) and 1.33□95%CI 1.09–1.63□ respectively(Figure3).

No differences in prevention of ischemic stroke were detected between warfarin versus aspirin in arterial origin stroke (RR,0.99,95%CI 0.85–1.15, $I^2 = 51.7\%$, $P = 0.126$), warfarin versus aspirin plus dipyridamole (RR,0.97,95%CI 0.66–1.14) and rivaroxaban versus aspirin (RR,1.02,95%CI 0.33–3.13) (Figure4). The major bleeding was significantly higher in the OACs group (RR,2.40,1.46–3.94) with the high heterogeneity ($I^2 =$

62.2%, P = 0.032). However, compared with aspirin, rivaroxaban did not increase the risk of major bleeding in Branch atheromatous stroke(Figure4).

The result of the funnel plot did not reveal small-study effects in this study with Harbord test (P = 0.299). We also performed a meta-regression to explore possible sources of heterogeneity in DOACs vs warfarin in AF, and then the intervention dose, rate of female and duration of follow-up could explain 75.36% sources of heterogeneity. The analysis with the exclusion of one study at a time, excluding the low dose edoxaban and dabigatran, the heterogeneity is 27%, excluding the study of RELY, the heterogeneity in subgroup of OAC plus aspirin vs OAC reached to 0.

Discussion

The key findings of this meta-analysis can be listed as follows. Firstly, DOACs was superior to warfarin and warfarin was superior to aspirin[14] for the prevention of stroke or systemic embolism in NVAF patients and did not increase the risk of major bleeding, OACs plus aspirin did not add benefit than OACs alone but a higher risk of major bleeding in NVAF patients. Therefore, DOACs alone was considered the optimal treatment for the prevention of stroke in NVAF. Secondly, there was no difference in warfarin versus aspirin in arterial origin stroke but with the higher risk of major bleeding. However, the efficacy and safety of rivaroxaban versus aspirin did not showed significant differences among branch atheromatous disease. This means that some anticoagulants such as DOACs could also be used in atherosclerotic disease if they could reduce the risk of bleeding. Therefore, we speculated that DOACs alone was enough to the secondary prevention for stroke in patients with NVAF with arterial origin stroke.

During the last few decades, the protocol of antithrombotic efficacy for secondary prevention in stroke had been shown to reduce the risk of ischemic events but at the cost of a parallel increase in the risk of bleeding. The current clinical practical recommended that the anticoagulation with OACs was the mainstay for cardiac stroke prevention in NVAF.[15] The network meta-analysis indicated that DOACs was superior to warfarin and warfarin was superior to aspirin or aspirin plus clopidogrel in reducing the risk of stroke events in NVAF.[16] OACs combined antiplatelet were only used in AF with acute PCI. While the real world or national registry trials showed that the large proportion of AF patients on combined OAC and antiplatelet therapy without atherosclerotic disease, and the major bleeding was significantly higher in the combination therapy and even no added benefits in ischemic events.[17,18] An exploratory analysis of SPORTIF suggested that the risks associated with aspirin plus anticoagulation in patients with AF outweigh the benefit.[19] Which was consistent with our meta-analysis that DOACs alone were recommended in NVAF.

Atherosclerotic disease was usually treated with antiplatelet therapy based on the pathophysiological concept of thrombus forming. The simple or dual antiplatelet therapy was recommended in ischemia stroke with atherosclerotic type or other arterial origin stroke. While previous studies attempted to prove that anticoagulation could be used as an alternative to antiplatelet therapy in atherosclerotic diseases.[20,8–10] It seemed that there was no difference between warfarin and aspirin for the prevention of recurrent ischemic stroke but with higher bleeding complications in warfarin. Therefore, aspirin was recommended in atherosclerotic disease because of the higher risk of bleeding in warfarin. A sub-analysis of NAVIGATE

ESUS confirmed rivaroxaban and aspirin had the same efficacy and safety in Branch atheromatous disease which was attributable to occlusion of proximal perforating arteries or of more than two adjacent perforating arteries due to atherosclerosis.[21] Previous network meta-analysis concluded that NOACs with edoxaban, apixaban and dabigatran 110 mg twice daily could reduce the risk of major bleeding compared with standard adjusted dose VKA.[16] Further RCTs are needed to explore safety of DOACs in atherosclerotic diseases.

Neurologists or clinicians were usually confused because it was complex about the individual's comorbidities. AF patients commonly had comorbidities with arterial diseases, sometimes prompting adding antiplatelet to anticoagulants based on higher risk of stroke. There was insufficient evidence to support combination therapy in AF with stable coronary artery disease.Large observational study indicated that combining warfarin and an antiplatelet increased the risk of bleeding without improving cardiovascular or ischemic outcomes.[22] Interestingly, a large part of the combination therapy was adopted. The combination was found in 30% of patients in ARISTOTLE[5] and 40% in RE-LY.[7] Subgroup analysis for these studies further confirmed that the combination therapy had a higher CHADS2 score than OACs alone.[23,24] CHADS2 or CHA2D2S-vasc score and HAS-Bled score were documented with high correlation. This meant that patients receiving the combination therapy had a higher risk for bleeding and ischemic stroke simultaneously. This may be a reason that combination therapy was not superior to OACs alone and with higher risk of bleeding in our meta-analysis.

The suboptimal combination therapy with low-dose warfarin plus aspirin did not provide a beneficial effect for reduction of stroke and major vascular events in AF patients at medium-risk but significantly increase the risk of bleeding.[10] Although the COMPASS trial[13] indicated that the combination of low-dose rivaroxaban and aspirin reduced major cardiovascular event. However, the population of COMPASS trial including very few AF patients had a low risk of cardiac-embolic stroke. Further RCTs will be needed to explore the efficacy and safety of combination therapy in AF with arterial origin stroke.

NVAF with chronic arterial diseases as comorbidities had higher risk of bleeding. There was no enough evidence to support combination therapy in clinical practice. DOACs could reduce the risk of major bleeding in NVAF and show the efficacy in NVAF and arterial origin stroke as discussed above. DOACs alone may be enough to prevent stroke recurrence and not to increase the risk of bleeding in the two comorbidities.

Our meta-analysis was limited in many aspects. Firstly, no RCTs directly evaluated the efficacy and safety of anticoagulants and antiplatelet for AF with arterial origin stroke. The conclusion of this meta-analysis was speculated. The indirect result need to be confirmed by RCTs in future. Secondly, subgroup data about combination therapy were not available in RCTs trial. Baseline characteristics were inconsistent which may result in potential heterogeneity. Thirdly, only published data were included, which may cause potential publication bias. Finally, only aspirin was included to evaluate and other antiplatelet agents may have other beneficial effects, such prospective data are needed.

Conclusions

The findings of this meta-analysis indicated that DOACs alone may be enough to prevent stroke recurrence and not to increase the risk of bleeding in AF patients with arterial origin stroke. In future, the well-designed RCTs would be need to confirm the efficacy and safety of different combination therapy with DOACs and antiplatelet agents or NOAC alone in AF with arterial origin stroke.

Abbreviations

AF:Atrial fibrillation; DOACs:Direct oral anticoagulants; OACs:oral anticoagulants; NVAF:non-valvular AF; PCI:percutaneous coronary intervention; RRs:relative risks; y,:year; m: month;d:day;BAD:Branch atheromatous stroke; W:warfarin; A:aspirin; D:dipyridamole

Declarations

Acknowledgements

None.

Consent to publish

Not applicable.

Author Contributions

GFF, LMX, and LH developed the study concept. SJK, LJJ,YQR, ZXL,ZY and TYB contributed to organizing data collection. GFF and LH contributed to data collection and design of the statistical analyses. GFF and LMX performed the statistical analyses. GFF and LMX wrote the first draft of the manuscript. LH, SJK, LJJ, and YQR reviewed and critiqued the statistical analyses and manuscript.

Funding

This work did not receive any specific grant from funding agencies in the public, commercial, or non-profit sectors.

Availability of data and materials

All data analyzed during this study are included in this article.

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Table

Table 1. Characteristics of studies included in the meta-analysis

study	blinding	country	mean age(y)	female no.	NO.in total	treatment VS control	type of quality event	follow-up	Jadad score
WARSS2001	double-blind	US	63	897	2206	W vs A	arterial origin	2 y	5
WASID2005	double-blind	America	63	219	569	W vs A	Intracranial Arterial Stenosis	1.8y	5
ESPRIT 2007	open label	multiple	61	322	1068	W vs A±D	arterial origin	4.6y	5
RE-LY2009	open label in warfarin	multiple	71	6598	18133	Dabigatran110or150mg vs W	atrial fibrillation	2.0y	5
ARISTOTLE2011	double-blind	multiple	70	6416	18201	apixaban 5mg twice vs W	atrial fibrillation	1.8y	5
ROCKET AF2011	double-blind	multiple	73	5663	14264	Rivaroxaban 20 or 5mgvs W	atrial fibrillation	707d	5
ENGAGE AF 2013	double-blind	multiple	72	8040	22105	Edoxaban 30or60mg vs W	atrial fibrillation	2.8y	5
NAVIGATE ESUS2019 sub2	double-blind	multiple	63	186	502	Rivaroxaban (15mg) vs A	BAD	11m	4

Abbreviations: y, year; m, month；d, day;BAD：Branch atheromatous stroke; W,warfarin; A, aspirin;D, dipyridamole

Figures

Figure 1

Flow chart of included/excluded studies

Figure 2

Forest plot for the efficacy outcomes of anticoagulants with or without antiplatelet therapy with different subgroups in NVAF patients

Figure 3

Forest plot for the major bleeding of anticoagulants with or without antiplatelet therapy with different subgroups in NVAF patients

Figure 4

Forest plot for the efficacy outcomes of anticoagulants versus antiplatelet therapy with different subgroups in arterial origin stroke

Figure 5

Forest plot for the major bleeding of anticoagulants versus antiplatelet therapy with different subgroups in arterial origin stroke

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