Efficacy and Safety of Direct Oral Anticoagulants (DOACs) Versus Warfarin in Atrial Fibrillation Patients with Prior Stroke: A Systematic Review and Meta-Analysis

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Introduction

Directly acting oral anticoagulants (DOACs) can be associated with lower ischemic stroke, systemic embolism (SE), intracranial hemorrhage (IH), major bleeding (MB) and mortality rates. Most systematic reviews and meta-analyses have assessed the efficacy and safety of DOACs in patients with Afib[1,2]. No systematic review and meta-analyses have examined DOACs for stroke prevention in Afib patients with a history of stroke in RCTs and OBSs studies.

Objectives

The purpose of our meta-analysis study was to investigate the efficacy and safety of all available DOACs vs. warfarin for stroke prevention in Afib patients with a history of stroke.

Methods

Data sources: Pubmed, Embase, The Cochrane Library and Clinical trials.gov.

Eligibility criteria for selecting studies: Published RCTs, OBSs evaluating the use of a DOAC vs warfarin, for stroke prevention patients with prior stroke.

Bias and Quality Assessment: Cochrane Collaboration tool for RCTs & Newcastle–Ottawa Scale for OBSs

Data analysis: CMA version 3 software was used to meta-analyze the selected studies. Dichotomous outcomes with safety and efficacy data were analyzed using hazards ratio (HR), and sample size to provide a pooled effect size between warfarin and DOAC groups. Pooled effect estimates were analyzed by the random-effects model using the DerSimonian–Laird method. RCTs were analyzed separately from OBSs. Subgroups of trials were treated as OBS studies as the randomization was broken, the two subgroups being compared were no longer exchangeable. Heterogeneity was assessed using the standard I^2statistics.

Results

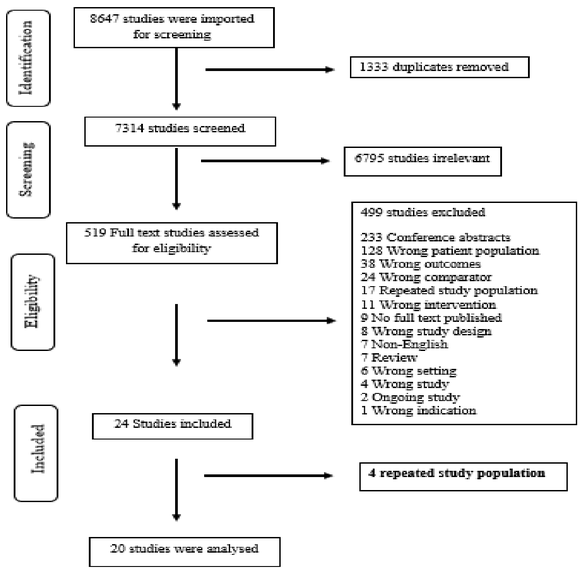

Figure1 : Process of study selection

Of the 8,647 articles screened, 24 studies were selected for systematic review. For meta-analysis, four studies were excluded as they were redundant claims or duplicate data, leaving 20 studies (1 RCT, 6 trail subgroups, 9 claims and 4 cohort) that were meta-analyzed. In all the 20 studies included in the meta-analysis patients had atrial fibrillation and history of transient ischemic stroke, ischemic stroke, or any kind of hemorrhagic stroke at baseline.

Comparing DOACs to warfarin, pooled HRs (95%CI) were consistently in favor of DOACs although some did not reach statistical significance: for ischemic stroke 0.84 (0.66-1.07) in claims; 0.90 (0.77-1.06) in non-claims and RCT subgroups; for systemic embolism 0.77 (0.62-0.96) in claims; 0.86 (0.77-0.96) in non-claims and RCT subgroups; for all-cause mortality 0.57 (0.33-0.99) in claims; 0.87 (0.79-0.96) in non-claims and RCT subgroups; for ICH 0.72 (0.39-1.33) in claims; 0.51 (0.38-0.67) in non-claims and RCT subgroups; and for major bleeding 0.86 (0.71-1.03) in claims; 0.90 (0.76-1.08) for non-claims and RCT subgroups.

Outcomes	RCTs Pooled HR (95%CI); # studies; p-heterogeneity; I^2 value	Claims studies Pooled HR (95% CI); # studies; p-heterogeneity; I^2 value	Non-claims and RCT subgroups Pooled HR (95% CI); # studies; p-heterogeneity; I^2 value
Efficacy Outcomes			
Ischemic stroke /transient ischemic attack	DL: 0.93 (0.06-14.51); 1 study p-hetero: NA; I^2: NA	DL: 0.84 (0.66-1.07); 6 studies; p-hetero: 0.00; I^2: 87.4%	DL: 0.90 (0.77-1.06); 6 studies; p-hetero: 0.75; I^2: 0%
Systemic embolism	NA	DL: 0.77 (0.62-0.96); 3 studies; p-hetero: 0.11; I^2: 55.4%	DL: 0.86 (0.77-0.96); 6 studies; p-hetero: 0.27; I^2: 21.9%
All-cause mortality	NA	DL: 0.57 (0.33-0.99); 3 studies; p-hetero: 0.00; I^2: 90.9%	DL: 0.87 (0.79-0.96); 7 studies; p-hetero: 0.86; I^2: 0%
Safety Outcomes			
Intracranial hemorrhage events	DL: 1.10 (0.70-1.72); 1 study p-hetero: NA; I^2: NA	DL: 0.72 (0.39-1.33); 4 studies; p-hetero: 0.35; I^2: 10.9%	DL: 0.51 (0.38-0.67); 8 studies; p-hetero: 0.00; I^2: 94.3%
Major bleeding events	NA	DL: 0.86 (0.71-1.03); 3 studies; p-hetero: 0.36; I^2: 2.46%	DL: 0.90 (0.76-1.08); 5 studies; p-hetero: 0.08; I^2: 51.8%

Table1: Pooled HR of efficacy & safety outcomes from studies comparing DOACs to warfarin, for each study design

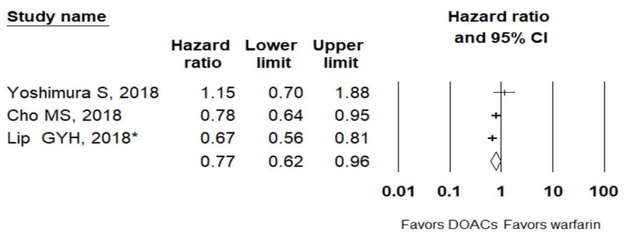

Figure 2 : Forest plot for Stroke/SE in claims

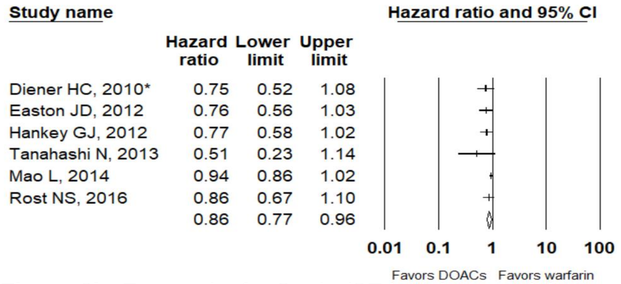

Figure 2b: Forest plot for Stroke/SE in cohort or trial subgroups

Discussion

Our analysis showed that DOACs were associated with lower risk of all cause mortality which was consistent with the study done by Adam et al[3]. Our analysis also revealed lower risk of recurrent stroke/ embolism among DOACs patients which was consistent with the results of Miller et al[4] There was inconsistent result between OBS claims and non-claims studies while evaluating the ischemic stroke/transient ischemic attack; this was probably due to the heterogeneity amongst the OBSs studies. Non-English studies were not included in this meta-analysis which may weaken the power of our meta-analysis study. However, our present study evaluated the safety and efficacy of DOACs vs warfarin in Afib patients with history of stoke in RCT, cohort and claims studies. This provided useful information of efficacy of drugs in a real world population in addition to controlled environment of RCTs.

Conclusions

DOACs were associated with better efficacy and safety profiles than warfarin in Afib patients with a stroke history; more specifically, a lower risk of SE, all-cause mortality, and IH. Further phase 3 clinical trials or well conducted comparative observational studies are still needed to confirm some of the non-statistically significant efficacy and safety endpoints.

Selected References

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•Adam, S. S., et al. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism: A systematic review. *Annals of Internal Medicine*, 2012; *157*(11), 796–807.

•Miller, C. S.,et al. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. *The American Journal of Cardiology*, 2012; *110*(3), 453–460.