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Comprehensive Systematic Review and Meta-Analysis on Anticoagulants and Aspirin for Stroke Prevention in Non-Valvular Atrial Fibrillation Patients

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ADMINISTRATIVE INFORMATION

Support - No.

Review Stage at time of this submission - Completed but not published.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 September 2023 and was last updated on 27 September 2023.

INTRODUCTION

Review question / Objective Non-valvular atrial fibrillation (NVAF) is a common manifestation of cardiac arrhythmia, whose significance is heightened in the context of an aging global population and changing lifestyles, leading to an increased incidence. Stroke prevention in NVAF is a complex challenge that requires a comprehensive exploration of interventions. The emergence of Direct Oral Anticoagulants (DOACs) is a potential treatment, necessitating a thorough evaluation of their safety and efficacy. As the quest for the best strategy for thrombotic risk in these patients continues, the interaction between DOAC and aspirin has become the focus of research. Methods: With a rigorous methodological approach, we conducted a thorough search of scientific databases up to August 2023. The methodology involved meticulous screening, careful data extraction, and rigorous assessment of trial quality, all conducted by two independent investigators. The results were synthesized through standardized mean differences, accompanied by 95% confidence intervals.

Condition being studied With a rigorous methodological approach, we conducted a thorough search of scientific databases up to August 2023. The methodology involved meticulous screening, careful data extraction, and rigorous assessment of trial quality, all conducted by two independent investigators. The results were synthesized through standardized mean differences, accompanied by 95% confidence intervals. DOACs demonstrated significant enhancements in stroke prevention for NVAF, which was indicated by favorable outcomes in bleeding (RR = 4.04, 95% CI: 3.96, 4.12), coronary

artery disease (RR = 2.45, 95% CI: 2.42, 2.48), mortality (RR = 0.49, 95% CI: 0.43, 0.56), myocardial infarction (RR = 1.85, 95% CI: 1.81, 1.88), and stroke (RR = 1.50, 95% CI: 1.47, 1.54). Notably, DOACs demonstrated optimal efficacy for NVAF patients with stroke. DOACs may be potentially effective for preventing stroke after NVAF.

METHODS

Participant or population This study strictly adhered to the established guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) for conducting a meta-analysis. Computer searches were conducted in databases including Cochrane Library, Embase, Web of Science, PubMed, China National Knowledge Infrastructure (CNKI), China Biology Medicine disc (CBM), and Wanfang Database.

Intervention (a) the realm of publication encompassed randomized controlled trials (RCTs) or observational studies; (b) a demographic scope of adult patients (≥18 years) was required, with a follow-up period of at least 3 months; (c) a meticulous comparison between DOAC alone and DOAC plus aspirin was sought, with a focus on safety and efficacy outcomes; (d) a comprehensive array of pivotal outcomes was explicitly reported, including major bleeding, myocardial infarction (MI), major adverse cardiac events (MACE), hospitalizations, all-cause mortality, stroke, or composite permutations thereof. (e) The study was conducted with a scientifically sound research design and adhered to standardized protocols. Follow-up data and other relevant information were comprehensively documented and completed.

Comparator This study has constructed a meta-analysis to explore the impact of DOACs on the risk of stroke following NVAF, contrasting relevant randomized controlled trials. In this analytical domain, DOACs may emerge as effective medications in preventing stroke after NVAF.

Study designs to be included (a) the realm of publication encompassed randomized controlled trials (RCTs) or observational studies; (b) a demographic scope of adult patients (≥18 years) was required, with a follow-up period of at least 3 months; (c) a meticulous comparison between DOAC alone and DOAC plus aspirin was sought, with a focus on safety and efficacy outcomes; (d) a comprehensive array of pivotal outcomes was explicitly reported, including major bleeding, myocardial infarction (MI), major adverse cardiac events (MACE), hospitalizations, all-cause mortality, stroke, or composite permutations thereof. (e) The study was conducted with a scientifically sound research design and adhered to standardized protocols. Follow-up data and other relevant information were comprehensively documented and completed.

Eligibility criteria The foundation of inclusion, fortified by a resonance spanning seven thematic dimensions, seamlessly converged to establish a robust threshold of scholarly eminence. The imperatives of our inclusion criteria were guided by distinct directives: (a) the realm of publication encompassed randomized controlled trials (RCTs) or observational studies; (b) a demographic scope of adult patients (≥18 years) was required, with a follow-up period of at least 3 months; (c) a meticulous comparison between DOAC alone and DOAC plus aspirin was sought, with a focus on safety and efficacy outcomes; (d) a comprehensive array of pivotal outcomes was explicitly reported, including major bleeding, myocardial infarction (MI), major adverse cardiac events (MACE), hospitalizations, all-cause mortality, stroke, or composite permutations thereof. (e) The study was conducted with a scientifically sound research design and adhered to standardized protocols. Follow-up data and other relevant information were comprehensively documented and completed.2.3 Exclusion Criteria(1) Case reports; (2) Studies lacking extractable relevant outcome measures, such as incidence rates; (3) Studies including patients with comorbid cross diseases2.4 Quality Assessment Criteria and Data ExtractionTwo independent reviewers conducted literature screening, data extraction, and quality assessment. Any discrepancies were resolved by a third reviewer. The data extracted in this study encompassed study design, study population, inclusion and exclusion criteria, intervention measures, treatment methods for the control group, and outcomes. Continuous data were extracted as means ± standard deviations (SD). For randomized controlled trials, the Jadad scale was used for quality assessment, while cohort studies and case-control studies were assessed using the Newcastle-Ottawa Scale (NOS) for quality assessment.

Information sources Within the timeframe from 2019 to August 2023, after meticulous research, a total of 732 relevant articles were obtained. After removing duplicate literature, 467 articles remained, including 315 in English and 152 in Chinese. Following a preliminary screening based on titles and abstracts, 440 articles were excluded, of which 154 were irrelevant to the research topic, 274 were case reports and reviews, and 12 were

single-group studies. After the initial screening, 27 articles were included. After reading the full texts, 10 articles were excluded, including 7 without specified data and 3 with participants' diagnoses not matching the criteria.

Main outcome(s) DOACs demonstrated significant enhancements in stroke prevention for NVAF, which was indicated by favorable outcomes in bleeding (RR = 4.04, 95% CI: 3.96, 4.12), coronary artery disease (RR = 2.45, 95% CI: 2.42, 2.48), mortality (RR = 0.49, 95% CI: 0.43, 0.56), myocardial infarction (RR = 1.85, 95% CI: 1.81, 1.88), and stroke (RR = 1.50, 95% CI: 1.47, 1.54). Notably, DOACs demonstrated optimal efficacy for NVAF patients with stroke.

Quality assessment / Risk of bias analysis Among the 17 studies included in this article, 12 were randomized controlled trials, and 5 were retrospective case-control studies. The quality of randomized controlled trials was evaluated using the Jadad scale, with appropriate random sequence generation (2 points), unclear allocation concealment (1 point), lack of blinding (0 points), and lack of description of withdrawals or dropouts (0 points), resulting in a Jadad score of 3 points, indicating low-quality literature.

Strategy of data synthesis Among the 17 studies included in this article, 12 were randomized controlled trials, and 5 were retrospective case-control studies. The quality of randomized controlled trials was evaluated using the Jadad scale, with appropriate random sequence generation (2 points), unclear allocation concealment (1 point), lack of blinding (0 points), and lack of description of withdrawals or dropouts (0 points), resulting in a Jadad score of 3 points, indicating low-quality literature.

Subgroup analysis 15 of the articles conducted detailed studies on bleeding. The results of the heterogeneity test showed significant heterogeneity among the studies ($I^2 = 100\%$, $p < 0.0001$), and a random-effects (RE) model was used. This evidence suggests that DOACs may be effective drugs for preventing bleeding symptoms in patients with NVAF after stroke (RR = 1.50, 95% CI: 1.47, 1.54),.

Sensitivity analysis Thirteen distinct articles converged to embark on the meticulous examination of symptoms related to coronary artery disease, revealing a landscape characterized by noticeable heterogeneity across each subgroup ($I^2 = 100\%$, $p < 0.0001$), necessitating the utilization of the RE model. The synthesis of this diverse body of evidence yielded a compelling revelation - DOAC emerges as an effective intervention in the alleviation of coronary artery disease in NVAF (RR = 2.45, 95% CI: 2.42, 2.48).

Country(ies) involved China.

Keywords Non-valvular atrial fibrillation; Stroke prevention; Anticoagulants; Aspirin; Meta-analysis.

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