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# Direct Oral Anticoagulants versus Vitamin K Antagonists for the Treatment of Atrial Fibrillation: Umbrella Review

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## ADMINISTRATIVE INFORMATION

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**Review Stage at time of this submission -** Preliminary searches.

**Conflicts of interest -** None declared.

**INPLASY registration number:** INPLASY202520048

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 9 February 2025 and was last updated on 9 February 2025.

## INTRODUCTION

**Review question / Objective** This study, through an umbrella systematic review, aims to comprehensively analyze the efficacy and safety of vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) in various atrial fibrillation (AF) patient populations. The study included systematic reviews and meta-analyses from the Embase, Medline, Cochrane, and Web of Science databases, strictly screening literature that met specific criteria and extracting relevant data. The research focused on key outcome indicators such as all-cause mortality, prevention of stroke or systemic embolism, and bleeding risks.

**Condition being studied** Patients with different atrial fibrillation (AF).

## METHODS

**Participant or population**

1.diagnostic criteria

The included literature in this study involved patients clinically diagnosed with atrial fibrillation , primarily based on electrocardiogram (ECG) or Holter monitoring, with typical findings of absent P waves, irregular f waves, absolutely irregular RR intervals, and normal QRS complex morphology. Clinically, patients may present with symptoms such as palpitations and chest discomfort, and auscultation may reveal an irregular heart rhythm and pulse deficit.

2.Inclusion criteria

The inclusion criteria for the study were as follows: the study population consisted of patients with AF, including those with comorbidities such as diabetes, end-stage renal disease, and venous

thromboembolism; the intervention involved the use of direct oral anticoagulants in the treatment group and vitamin K antagonists in the control group, with a defined treatment duration for both groups; outcome measures included stroke or systemic embolism, total bleeding events, life-threatening or major bleeding events, intracranial hemorrhage, gastrointestinal bleeding, significant bleeding, minor bleeding, bleeding stroke, serious bleeding, and all-cause mortality; and the study design was meta-analyses or systematic reviews and meta-analyses.
3.Exclusion criteria
The exclusion criteria included: literature reporting on pregnant or lactating women, or those with drug allergies; study types such as conference papers, animal experiments, or clinical trial protocols; literature published in languages other than English; literature that could not be obtained in full text; literature with erroneous, incomplete, or unobtainable data; and literature with repeated publication of the same data.

**Intervention** Direct Oral Anticoagulants.

**Comparator** Vitamin K Antagonists.

**Study designs to be included** Meta.

**Eligibility criteria** The included literature in this study involved patients clinically diagnosed with atrial fibrillation , primarily based on electrocardiogram (ECG) or Holter monitoring, with typical findings of absent P waves, irregular f waves, absolutely irregular RR intervals, and normal QRS complex morphology. Clinically, patients may present with symptoms such as palpitations and chest discomfort, and auscultation may reveal an irregular heart rhythm and pulse deficit.

**Information sources** Embase; pubmed; Cochrane; Web of Science.

**Main outcome(s)** All-cause mortality: Evaluate the effectiveness of vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) in reducing all-cause mortality in patients with atrial fibrillation.
Prevention of stroke or systemic embolism: Compare the effectiveness of VKAs and DOACs in preventing stroke or systemic embolism in patients with atrial fibrillation.
Bleeding risks: Assess the safety of the two anticoagulant drugs in reducing bleeding events, including major bleeding, minor bleeding, and gastrointestinal bleeding.

**Quality assessment / Risk of bias analysis** AMSTAR 2 and GRADE.

**Strategy of data synthesis** For each meta-analysis, the extracted relevant data was presented in tables, and effect sizes such as OR and RR 95% CI were extracted. A heterogeneity standard of $I^2 \geq 50.0\%$ or $P < 0.10$ was considered to have significant heterogeneity. Finally, a comprehensive qualitative analysis of the data from the included studies was conducted, combining text with charts and graphs.

**Subgroup analysis** Define Subgroups: Based on the characteristics of the study population, intervention, or outcome, define subgroups. For example, in the context of atrial fibrillation patients, subgroups can be defined according to age (elderly vs. non-elderly), comorbidities (such as diabetes, cancer, renal insufficiency, coronary heart disease), and other relevant factors.
Conduct Analysis: Perform the analysis within each subgroup. This involves extracting relevant data from the included systematic reviews and meta-analyses and calculating the effect sizes and their confidence intervals for each subgroup. For instance, compare the efficacy and safety of VKAs and DOACs in patients with non-valvular atrial fibrillation who have diabetes versus those without diabetes.
Compare Results: Compare the results between different subgroups to identify any differences in the efficacy and safety of the interventions. For example, if DOACs show a significant reduction in all-cause mortality in elderly patients with non-valvular atrial fibrillation but not in younger patients, this suggests that age may be a factor influencing the effectiveness of the treatment.
Interpret Findings: Interpret the findings in the context of clinical relevance and potential reasons for the observed differences. For example, if a certain comorbidity is associated with a better response to DOACs, it may be due to the specific pathophysiological mechanisms of that comorbidity.

**Sensitivity analysis** Select Variables: Choose the variables that may affect the results of the review. These can include methodological quality of the included studies, sample size, publication year, and other factors that may introduce bias or heterogeneity.
Perform Analysis: Conduct the analysis by excluding studies with certain characteristics or by changing the analysis model. For example, exclude studies with high risk of bias or those published before a certain year, and then re-evaluate the results.

Compare Results: Compare the results of the sensitivity analysis with the original analysis to see if there are any significant changes in the effect sizes or conclusions. If the results remain consistent, it suggests that the findings are robust and reliable.
Interpret Findings: Interpret the findings of the sensitivity analysis in terms of the impact of the selected variables on the results. For example, if excluding low-quality studies does not change the overall conclusion, it indicates that the results are not driven by the methodological quality of individual studies.

**Country(ies) involved** China.

**Keywords** umbrella systematic review; systematic review; atrial fibrillation; vitamin K antagonists; direct oral anticoagulants.

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