# Tolerability and Acceptability of Non-Vitamin K Antagonist Oral Anticoagulants in Atrial Fibrillation: Systematic Review and Meta-Analysis

**American Journal of Cardiovascular Drugs volume 15, pages 259–265(2015)**

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**Abstract**

Background

The non-vitamin K antagonist oral anticoagulants (NOACs) overcame some limitations of vitamin K antagonists (VKAs), and are at least as effective in stroke prevention, with an additional decrease of intracranial bleeding risk. The transferability of these benefits to the real world requires tolerability (related to adverse events) and acceptability (drug discontinuation) profiles at least similar to VKAs.

Methods

We performed a systematic review with meta-analysis of randomized controlled trials (RCTs) evaluating NOACs versus VKAs in patients with non-valvular atrial fibrillation (AF). Studies were searched in April 2015 through MEDLINE, the Cochrane Collaboration's Database, Health Technology Assessment (HTA), Web of Science, and regulatory agencies' documents. Serious adverse events (SAEs) as well as drug-related and patient-related discontinuation rates were the outcomes of interest. Random-effects meta-analysis was performed, and the results expressed as risk ratios (RRs) and 95 % confidence intervals (CIs). Heterogeneity was evaluated with I 2 test.

Results

Five RCTs evaluating four NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) and 72,720 patients were included. Overall, NOACs were associated with a 4 % risk reduction of SAEs (95 % CI 2–6; I 2 = 0 %). Drug-related and patient-related discontinuation rates were similar between NOACs and VKAs (RR 1.03 [0.88–1.21] and RR 0.99 [0.89–1.10], respectively). Significant heterogeneity (I 2 ≥ 75 %) was found among studies results, which could be, at least partially, explained by the findings of the open-label dabigatran trial.

Conclusions

NOACs were associated with a small, yet significant, risk reduction of SAEs in patients with AF. NOACs' drug-related and patient-related acceptability profiles were similar to those for VKAs. The results were heterogeneous mainly because of the increased rate of discontinuation associated with dabigatran. Pragmatic trials and cohort studies should be conducted to further address these important clinical questions.

**Keywords**
Atrial Fibrillation, Dabigatran, Venous Thromboembolism, Rivaroxaban, Apixaban