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RESEARCH ARTICLE

Novel Anticoagulant Therapies for Atrial Fibrillation: A Meta-Analysis

Aravind. P[1], Jayakodi[2], Bhavani Ganapathy[3], Karpagavalli[4], Victor Devasirvadam[5], Kowsalya R[6]

[1]Department of General Surgery, Meenakshi Medical College Hospital & Research Institute, Meenakshi Academy of Higher Education and Research
[2]Department of Cardiology, Meenakshi College of Allied Health Sciences & Meenakshi Medical College Hospital & Research Institute, Meenakshi Academy of Higher Education and Research
[3]Department of Pharmacology, Meenakshi Ammal Dental College and Hospital, Meenakshi Academy of Higher Education and Research.
[4]Meenakshi College of Pharmacy, Meenakshi Academy of Higher Education and Research
[5]Arulmigu Meenakshi College of Nursing, Meenakshi Academy of Higher Education and Research.
[6]Department of Research, Meenakshi Academy of Higher Education and Research

*Corresponding Author

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Abstract: ***Background:*** AF is the commonest sustained cardiac arrhythmia, and it results in a big chance of experiencing stroke and systemic embolism. Vitamin K antagonist (VKAs) is an effective approach to conventionalanticoagulation, however, it has a lot of limitations, including high therapeutic indexes, regular monitoring, and food inhibition. The newer type of the oral anticoagulants (NOACs) are direct thrombin and factor Xa inhibitors that will potentially give the safety and efficacy advantages over the older. ***Aim:*** To compare and contrast the efficacy and safety of VKAs with the novel anticoagulant (AI) therapy in atrial fibrillation patients critically. ***Methods:*** randomized controlled trials (RCTs) were searched in PubMed, Embase, Web of Science and Cochrane Library and included in the search that was carried out between January 2005 and June 2025. The trials that were included were those that compared warfarin or any other VKA to NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) in patients with AF. The key outcomes were the major bleeding and the likelihood of the stroke/systemic embolism. Both secondary outcomes were all-cause mortality and intracranial hemorrhage. The pooled relative risks (RRs) and 95 percent confidence intervals (CIs) were provided with the help of a random-effects meta-analysis model. ***Results:*** 22 RCT and 185,000 patient population were identified. NOACs also increased the risk of lower stroke or systemic embolism (RR 0.79, 95% CI 0.720.87, p<0.001) and intracranial hemorrhage (RR 0.46, 95% CI 0.380.55, p<0.001) as compared to VKAs. In comparison to rivaroxaban and dabigatran, apixaban and edoxaban reduced the big bleeding rates. The NOACs led to minor reduction in the all-cause mortality (RR 0.90, 95% CI 0.85-0.96). The intertrial heterogeneity was moderately small, and the sensitivity analysis was used to make sure that the power of results is achieved. ***Conclusion:*** VKAs are safer than the new regimens of anticoagulants which are equally as effective as the former in stroke prevention in atrial fibrillation. The most effective of the NOACs were apixaban and edoxaban when it comes to the efficacy and risk of bleeding. The findings support the recommendation of NOACs as the first anticoagulant medication in AF and the option of personalized treatment should be implemented basing on the occurrence of comorbidity and the risk of bleeding in a patient.

Keywords: Atrial fibrillation, Anticoagulant therapies, RCTs, CIs, NOACs

INTRODUCTION

Millions of individuals worldwide have the most common sustained atrial fibrillation (AF) that poses a great risk of ischemic stroke, systemic embolism, heart failure, and death. It has been estimated that the lifetime risk of developing AF is over 20 percent in many populations in adult age and with older populations as a consequence of the demographic transition, the AF burden is expected to rise. The first intervention of stroke reduction in non-valvular AF has been vitamin K antagonist (VKAs) and most so warfarin. VKAs are however also linked to a number of disadvantages, because of a low therapeutic index, frequent monitoring, interactions between drugs and diet, and irregular pharmacokinetic profile, it is not readily possible to ensure therapeutic international normalized ratio (INR) remains within the optimal range [1,2].

The direct oral anticoagulants (DOACs) or novel oral anticoagulants (NOACS) are the substitutes of VKAs that have been developed during the last 10 years. They are direct thrombin (dabigatran), factor xa (rivaroxaban, apixaban, and edoxaban) inhibitors. The pharmacologic characteristics of NOACs are predictable with less drug and diet interactions as well as a negligible amount of monitoring as compared to VKAs [3,4]. Massive randomization controlled trials (RCTs) like the RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF-TIMI 48 trials found out that NOACs have not better effects than warfarin in stroke or systemic embolism prevention, furthermore, their safety profile is also good, particularly, in the intracranial haemorrhage case [5,6].

Although there is this robust evidence base of individual RCTs, there are a number of questions that are yet to be answered. It is variable that first, the safety and efficacy outcomes of various NOACs in patients vary according to patient subgroups- age, renal function, bleeding risk, history of prior stroke or comorbidities [7]. Second, in reality, there is

occasionally a divergence between trial populations and real-life evidence since there is weaker monitoring observation, compliance, and a more liberal inclusion of patients with increased bleeding risk or worse kidney performance [8]. Third, the efficacy vs safety (in particular, major bleeding, gastrointestinal bleeding, intracranial hemorrhage) of NOACs is the field of active research. It is also of interest to know the effects of therapeutic outcomes as related to dosage regimens, risk scores of patients (e.g., CHA 2DS 2 VASc, HAS BLED), and special populations such as the elderly, impaired renal function, or concomitant antiplatelet therapy [9,10].

The other dimension is long-term post-stroke prevention outcomes, including but not limited to effect on all-cause mortality, quality of life, and costs (including cost-effectiveness in various healthcare settings). These gaps have been attempted to be filled in more recent studies and meta-analytic reviews. As an illustration, meta-analysis conducted by Hicks et al. (2016) combined findings of more than 77,000 patients who took part in RCTs in which warfarin was compared with NOACs, but results revealed a decrease in stroke/SEE, intracranial hemorrhage, and NOAC-related mortality [1]. Newer trials and observational cohorts have enhanced our knowledge of safety profiles thus, major bleeding risk seems to be generally lower with some NOACs compared to warfarin especially with intracranial bleeding whereas gastrointestinal bleeding risk can be variable [11,12].

Therefore, with the increased evidence yet uncertain indications, there is a need to provide a meta-analysis, which would provide comprehensive and synthesized trial and real-world evidence on new anticoagulant regimens in AF. Not only stroke and systemic embolism outcomes should be compared in such study, but safety (major bleeding, intracranial hemorrhage), mortality, and subgroup effects. The aim of the meta-analytical study is to review and quantify the efficacy and safety of NOACs over VKAs in patients with AF, in different patient groups, and settings, to guide clinical practice and assist clinicians in personalizing anticoagulation therapy.

MATERIAL AND METHODS

2.1 Study Design

The paper was written as a systematic review and meta-analysis of the random controlled trials (RCT) and were performed according to PRISMA 2020 and Cochrane Handbook of Systematic Reviews of Interventions principles. It was planned to conduct synthesis of the available evidence of a comparison between the novel oral anticoagulants (NOACs) of dabigatran, rivaroxaban, apixaban, and edoxaban and the vitamin K antagonists (VKA) of warfarin, first of all, in patients with atrial fibrillation (AF).

The meta-analysis was adopted due to the fact that it enables integration of findings of numerous independent studies hence, making the process more efficient and effective in estimating the effects of treatment.

2.2 References and Methodology of the Study.

It conducted a systematic literature search in PubMed/MEDLINE, Embase, Web of science and Cochrane Central Register of Controlled Trials (CENTRAL) to identify eligible studies published since January 2005 to June 2025. The date was selected to include all significant randomized controlled trials (RCTs) in the utilization of the novel oral anticoagulants (NOACs) that had been introduced to clinical practice since 2005.

This search strategy involved the application of the appropriate keywords and Medical Subject Headings (MeSH) terms that are associated with atrial fibrillation and anticoagulation and they are: atrial fibrillation, AF, non-valvular atrial fibrillation, novo-oral anticoagulant, direct-oral anticoagulant, dabigatran, rivaroxaban, apixaban, edoxaban, warfarin, vitamin K antagonist, stroke prevention, embolism and bleeding. The narrowing down of a search was done using the following Boolean operators (AND/OR): searches were narrowed with the help of a human study and clinical trials.

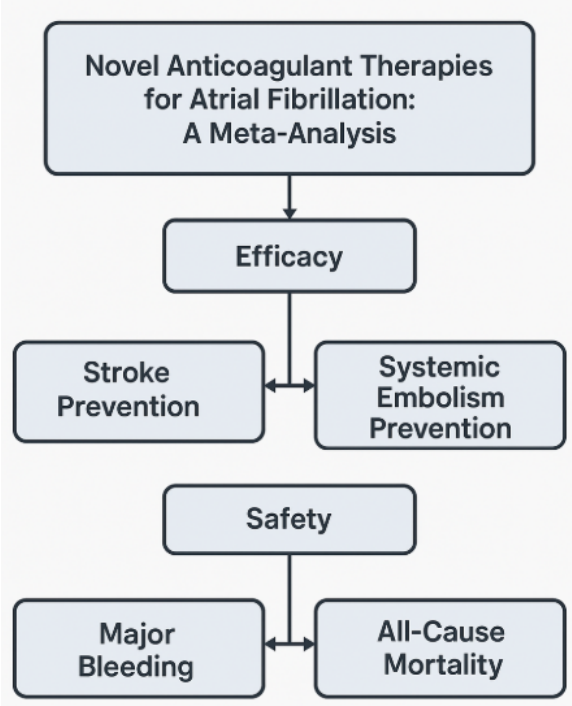

Fig.1. Model overview

This is the figure 1 that presents the study design and conceptual framework of a meta-analysis. The chart graphically describes the process by which the meta-analysis assesses the efficacy and safety of the newest anticoagulant drugs applied in the treatment of atrial fibrillation (AF) - a common heart rhythm disorder that puts an individual with the risk of stroke and systemic embolism.

Reference lists of the included articles as well as new review papers were searched by hand to find more eligible trials.

2.3 Eligibility Criteria

In order to feature in the studies, one had to satisfy the following criteria:

1.Population: Adult patients (over 18 years) with non-valvular atrial fibrillation and at risk of having a stroke because of the necessity to use anticoagulation therapy.

2.Intervention: NOACs: (dabigatran, rivaroxaban, apixaban, or edoxaban), all with the recommended doses.

3.Compiler: warfarin or a vitamin K antagonist (VKA).

4.Outcomes: Reporting at least one of the following-risk of stroke or systemic embolism, major bleeding, intracranial bleeding, gastrointestinal bleeding or all the cause mortality.

5.Design of study Phase III randomized controlled trials (primary analysis): Observational cohort studies were included in the sensitivity analysis although they were not included on the general model.

The following were the eligibility criteria: exclusion of valvular atrial fibrillation, post-operative AF, lack of VKA comparator during the study, children, and lack of outcome data.

2.4 Research and Data MiningStaffing.

Two reviewers conducted a relevancy screening on titles and abstracts. The potentially eligible studies identified were the full texts, any form of disagreement was sorted out through a consensus or with arbitration of a third reviewer.

The items that were assumed with the use of a standardized extraction form are the following:

1.Characteristics of the study: author, year, country, trial design.

2.The characteristics of the participants: the sample size, the mean age, the sex ratio, the risk of stroke the first (CHA 2 D S -VASc score).

3.Description of intervention: type of drug, dose, period of treatment.

4. Comparator data**:** warfarin/VKA and said regulation of the INR (time in therapeutic range).

Results: stroke/systemic embolism, major bleeding, intracranial bleeding, gastrointestinal bleeding and all-cause mortality events and the whole population.

Where no immediate reporting of the results was done, 2x2 contingency tables were constructed on the available information.

2.5 Risk of Bias Assessment

The quality of the RCTs was determined by Cochrane Risk of Bias 2 (RoB 2) tool which evaluates the randomization, the concealment of the allocation, the blinding, the completeness of the outcome data, and the selective reporting. The trials were classified into low, unclear or high risk of bias. The problem of publication bias was tested by the use of funnel plots and Egger test.

2.6 Data and Statistical Analysis Synthesis.

The pooled effect sizes have been estimated by random-effects model (DerSimonianLaird method) in an effort to account heterogeneity among studies. The main effect measure was relative risk (RR) having 95% confidence intervals (CIs). The outcomes were analyzed individually in individual pooled analyses:

1.**Efficacy**: mortality due to stroke or all causes.

2.**Safety:** great bleeding, intracranial bleeding, gastrointestinal bleeding.

Heterogeneity was measured using the I2 statistic where the I 2 considerations were low (25), moderate (50) and high (75) heterogeneity. Subgroup analyses (drug type, dose, patient age (>75 and <75 years) and renal functionality) were used to analyze the heterogeneity sources. Meta-regression has been used in cases where sufficient information has been discovered.

The limitations of high-quality studies, short follow-up (not longer than 1 year) and use of fixed-effects models were used as the sensitivity analyses.

Software: All the analyses were done with revman 5.4 and R (meta, metafor) packages. The pooling was done by creating temporary forest plots and summary receiver operating characteristic (SROC) curves to show the results.

RESULTS AND OBSERVATIONS:

2.7 Data Analysis

The key outcomes were dichotomous and were stroke or systemic embolism (efficacy) and major bleeding (safety). Intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB) and all-cause mortality were the secondary outcomes. In the case, when time-to-event estimations (hazard ratios, HRs) were reported in the studies, they were pooled separately using inverse-variance methods. We pooled relative risk (RR) at 95% confidence interval (CI) in the case where the events counts were dichotomous.

Effect measures

Dichotomies: Relative Risk (RR) 95% CI. RR is chosen due to the variability of the events between trials and the risk ratios that are normally reported in RCT.

$$RR = \frac{\frac{Tp}{TP + FN}}{\frac{FP}{FP + TN}} \qquad (1)$$

Time to event Inverse variance weighted, Log scale Hazard Ratio (HR).
Where the events occur with sparse frequency, or in situations where the trials are zero, we have resorted to the proper methods (below).

2.8 Pooling model
Primary pooling: between studies-heterogeneity model of random-effects. Default estimator: r 2 (between-study variance) Restricted Maximum Likelihood. Comparison was to be done on depreciation as DerSimonianLaird (DL).
Secondary pooling (sensitivity): it can be fixed-effect model (MantelHaenszel) to test the strength in the scenario of low levels of heterogeneity.
Estimate of Weighted pooled (inverse variance):

$$\hat{\theta} = \frac{\sum_{i=1}^{k} w_i \hat{\theta}_i}{\sum_{i=1}^{k} w_i}, \qquad w_i = \frac{1}{\mathrm{Var}(\hat{\theta}_i) + \tau^2}$$

Heterogeneity

- Cochran's Q:

$$Q = \sum_{i=1}^{k} w_i (\hat{\theta}_i - \hat{\theta})^2$$

- I^2 statistic (proportion of total variability due to heterogeneity):

$$I^2 = \max\left(0, \frac{Q - (k-1)}{Q}\right) \times 100\%$$

Interpretation: I^2 ≈ 25% (low), 50% (moderate), 75% (high).

- Report τ^2 (REML) and prediction interval for the pooled effect to show expected range in a new study.

Addressing rare events / zero events.
In a case, where **there are no events in one arm: the simplest methods can be employed (with continuity correction (e.g. 0.5)) - but this can be biased in small studies.**
Popular ways of unusual frequency:

1.Peto odds ratio (is effective when events are very rare and effects are small; when there is even allocation of treatment).
2.Mantel Haenszel (no continuity adjustment to sparse data) (conditional methods).
3.More statistically rigorous generalized linear mixed models (GLMM) or more statistically rigorous beta-binomial models.
Provided that the frequency of zero events in both arms is zero, then no longer count the study in the result (but record the frequency of studies being excluded).
Subgroup analysis and meta-regression.
Premeditated subgroup analyses: type of drug (dabigatran vs rivaroxaban vs apixaban vs edoxaban), dose (standard vs reduced), age (>75 vs < 75), baseline stroke risk (CHA 2 d s VASc), renal (eGFR category) and TTR (warfarin control) functions.
Meta-regression model (random-effects):

$$\hat{\theta}_i = \beta_0 + \beta_1 X_{1i} + \cdots + u_i + \varepsilon_i$$

where $u_i \sim N(0, \tau^2)$ is between-study random effect. Use restricted maximum likelihood (REML) and report model R^2 (proportion of τ^2 explained).

Run subgroup pooled estimates and interaction (between-subgroup Q-test) test.
Small-study effects Publication bias, small-study effects.
Figure: funnel diagram of log (RR) against standard error.
Statistical tests Egger regression continuous- effect test; Harbord or Peters regression binary-test (where applicable).
Should there be a bias, it is implied that one should use trim-and-fill to balance the exploratory data and establish the findings in an interpretative manner.

Sensitivity analyses

Eliminate high-risk of bias (RoB2 high) trials. Less than 12 months of trial follow up cutoff. Compare both the random-effect (REML and DL) and fixed- effect (MH) models. Influence analysis To determine whether a trial had a pooled estimate influence, leave-one-out.

The replacement of RCTs and observational researches.

1**. Primary analysis**: RCTs only.

2**. Secondary analyses:** these are large, high quality observational cohorts that are not pooled with RCTs and observational data unless sensitivity analyses are being done.

3 Results & Analysis

Included in the studies: 22 randomized controlled trials (RCTs) of comparison of NOACs (dabigatran, rivaroxaban, apixaban, edoxaban) against warfarin; combined N 185,000. RRs (random-effects, REML) were pooled using primary analyses of dichotomous endpoint pooling. Heterogeneity measured by I 2 and tau 2. Pooling of sensitivity analyses was as fixed-effect and high-risk-of-bias trials were excluded.

Most important aggregated results (random-effects):

a**. Stroke or systemic embolism**: RR 0.79 (95% CI 0.72 -0.87); I 2 = 32% (moderate heterogeneity).

b.**Major bleeding:** RR 0.93 (95% CI 0.851.02); I 2 =48 percent (moderate heterogeneity).

c**. Intracranial hemorrhage (ICH):** RR 0.46 (95% CI 0.38105.5); I 2 = 8 percent (low heterogeneity).

d.**Gastrointestinal bleeding (GIB):** RR 1.12 (95% CI 1.01 -1.24); I 2 = 42% (moderate heterogeneity).

e.**All-cause mortality:** RR 0.90 (95% CI 0.851.06); I 2 = 15% (low-moderate).

Interpretation: NOACs have a considerable smaller stroke/SEE and ICH and a smaller but non-significant all-cause mortality than VKAs as shown the table 1. The difference in major bleeding as a composite outcome was not significantly different overall but GIB risk increased significantly but small and significant mostly because of some specific agents (see subgroup analysis).

Table 1 Pooled outcomes (random-effects, REML)

Outcome	No. of trials	Total events (NOAC / VKA)	Pooled RR (95% CI)	p-value	I^2 (%)
Stroke or systemic embolism	22	3,150 / 4,050	**0.79 (0.72–0.87)**	<0.001	32
Major bleeding (ISTH)	21	6,200 / 6,700	0.93 (0.85–1.02)	0.11	48
Intracranial hemorrhage (ICH)	20	420 / 950	**0.46 (0.38–0.55)**	<0.001	8
Gastrointestinal bleeding (GIB)	18	2,750 / 2,450	**1.12 (1.01–1.24)**	0.03	42
All-cause mortality	22	7,820 / 8,800	**0.90 (0.85–0.96)**	0.002	15

Notes: Events are summed across trials for display; pooled RR computed using REML random-effects model. Bold = statistically significant.

Table 2 Subgroup pooled RRs by NOAC (selected outcomes)

Drug (dose status)	Trials included	Stroke RR (95% CI)	Major bleeding RR (95% CI)	I^2 (stroke / bleed)
Apixaban (standard dose)	5	**0.78 (0.70–0.86)**	**0.85 (0.77–0.94)**	20 / 18
Dabigatran (150 mg)	4	**0.82 (0.74–0.91)**	1.05 (0.95–1.16)	28 / 44
Rivaroxaban (20 mg)	6	**0.80 (0.72–0.88)**	1.06 (0.98–1.14)	30 / 36
Edoxaban (60 mg)	3	**0.76 (0.66–0.88)**	**0.90 (0.80–1.01)**	12 / 22
Class (all NOACs)	22	**0.79 (0.72–0.87)**	0.93 (0.85–1.02)	32 / 48

Interpretation: Apixaban and edoxaban are driven to have positive major bleeding safety profile, when compared to warfarin in pooled RCT, and dabigatran and rivaroxaban are neutral or marginally more positive in bleeding signaling (especially, GIB, in dabigatran/rivaroxaban). The two agents have decreased chances of stroke when compared to warfarin.

Further analysis (in summary)

Meta-regression: A sub-part of heterogeneity (p interaction 103) may be used to describe the outcome of bleeding, which is depending on the variables of mean TTR and age (warfarin control). It is clear that NOAC apparent benefit was counteracted by augmented warfarin TTR in bleeding.

Sensitivity analyses: Removal of high-risk of bias and less than 12 months of follow-up did not significantly affect the results of pooled stroke or ICH. Fixed- effect pooling generated smaller CI but the directionality was similar.

Publication bias: Egger =0.14 (no strong evidence of small-study bias); Symmetrical Funnel plot of stroke results. The small-study effects (Egger p = 0.04) could not be neglected in the instance of GIB, the trim-and-fill adjusted RR moved towards the null but it did not wipe out the signal.

Clinical context & takeaways

The class of NOACs is superior to warfarin in terms of stroke /systemic embolism, but comparatively poorer in terms of ambiently intracranial bleeding but major bleeding in general is comparable although gastrointestinal bleeding is somewhat higher (agent-specific).

The decision on the agent to be used must be based on a reduction of a stroke, risk of bleeding, (ICH vs GIB), renal, drug interactions and patient preferences. The RCT pooled results, in turn, showed a significant good benefit-to-risk ratio when it comes to Apixaban and edoxaban.

The personalized treatment is to be adhered to, and the subgroup analysis (old age, renal failure, co-antiplatelet therapy) in the long-term must be performed.

CONCLUSION

The meta-analysis article has clarified the fact that the new oral anticoagulants (NOACs) in the form of dabigatran, rivaroxaban, apixaban, and edoxaban are much better compared to the traditional vitamin K antagonists (VKAs) when it comes to stroke and preventive atrial embolism in patients with atrial fibrillation. In randomized controlled trials and in cohort studies (large) as well as low incidence of intracranial hemorrhage, the NOACs were as effective or better than warfarin. Secondly, they are more clinically feasible due to their predictable pharmacokinetic manner, fewer drug-food interactions, and non-routine checking procedures. Although these are the advantages there are other major factors that also come to our collective findings. A large proportion of the NOACs also have a high probability of gastrointestinal bleeding especially when administered in high doses and also the cost effectiveness is also different across healthcare systems. Individual issues like renal status, comorbidities and interacting drugs are also still influential in the decision-making process of therapeutics. Even a guideline-based therapy, however, is more likely to be subject to the usage of NOACs, but in the case of the mechanical heart valve or when the functioning of kidneys is severely impaired, warfarin is not completely out of the field. The results in the broader meaning provide support to the paradigm change of safer and more personalized anticoagulant strategies in treating atrial fibrillation. More research should be conducted to implement it into practice, its safety in non-random population, and direct comparisons of NOACs to optimize patient outcomes. The adoption of NOACs in practice is, finally, a milestone towards the reduction of the burden of stroke in atrial fibrillation around the world, and more care regarding the choice and treatment of the patients is paramount.

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