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Original Research Article

Comparing Effectiveness and Safety of Non-Vitamin K Antagonist Oral Anticoagulants to Warfarin in Atrial Fibrillation Patients: A Retrospective Study

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Abstract:

Background: Non-vitamin K antagonist oral anticoagulants (NOACs), also known as direct oral anticoagulants (DOACs), have transformed the management of atrial fibrillation (AF), offering an alternative to the long-established vitamin K antagonist warfarin. The study compares NOACs and warfarin for atrial fibrillation patients' primary and secondary outcomes. The study also examined anticoagulant therapy results by BMI and BW.

Methods: The study included 464 individuals who met the inclusion criteria of confirmed AF diagnosis and participation in relevant trials. Data on primary efficacy and safety outcomes were collected, alongside secondary outcomes. Statistical analysis assessed the association between therapies and clinical outcomes across different BMI and BW categories.

Results: The study comprised 464 AF patients with average age of 68.5. Baseline parameters were similar for NOAC and warfarin. A stroke or systemic embolic event occurred in 15.2% of NOAC patients and 18.9% of warfarin patients ($p = 0.312$). The NOAC group had 8.7% major bleeding events and the warfarin group 11.2% ($p = 0.481$). Secondary outcomes including ischemic stroke/SEE, cerebral haemorrhage, death, and net clinical outcomes did not differ across groups. No significant variations in outcomes were seen between NOAC and warfarin groups by BMI and BW.

Conclusion: NOACs demonstrated similar efficacy and safety profiles contrast to warfarin in atrial fibrillation patients, with no significant variations in stroke/SEE and major bleeding rates. Secondary outcomes and stratified analyses by BMI and BW further support the comparability of NOACs and warfarin.

Recommendations: Further studies should continue to evaluate the long-term outcomes of NOACs in diverse patient populations and explore strategies to improve accessibility to NOACs given their higher costs. Ensuring the availability of reversal agents for NOACs remains critical in managing bleeding complications effectively.

Keywords: Non-vitamin K antagonist oral anticoagulants, Warfarin, Atrial fibrillation, Stroke prevention, Anticoagulation therapy.

Introduction

Direct oral anticoagulants (DOACs), another name for non-vitamin K antagonist oral anticoagulants (NOACs), have revolutionised the treatment of atrial fibrillation (AF) by providing a substitute for the well-established vitamin K antagonist warfarin. When compared to warfarin, NOACs—which include medications like dabigatran, rivaroxaban, apixaban, and edoxaban—are recommended more frequently because of their predictable pharmacokinetics, less dietary restrictions, and less requirement for routine monitoring [1]. Because of these qualities, NOACs are a desirable alternative for preventing stroke and systemic embolism in patients with AF, appealing to both patients and healthcare professionals.

The most prevalent prolonged cardiac arrhythmia, atrial fibrillation, greatly raises the risk of thromboembolic events, especially ischemic stroke. In patients with AF, effective anticoagulation is essential for preventing stroke, and warfarin has long been the cornerstone of care. However, there are a number of drawbacks to warfarin therapy, such as a limited therapeutic range, substantial variability both within and between patients, a high number of food and drug interactions, and the need

for routine international normalised ratio (INR) monitoring to ensure both therapeutic efficacy and safety [2].

Dabigatran inhibits thrombin (factor IIa), whereas rivaroxaban, apixaban, and edoxaban inhibit factor Xa. These are the specific coagulation factors on which NOACs directly act [3]. Because of its focused mode of action, anticoagulants have a more predictable impact, making dosing schedules easier to follow and obviating the need for frequent coagulation monitoring. Furthermore, NOACs improve patient adherence and quality of life because they interact with meals and other medications less frequently.

Studies conducted in the real world and clinical trials have shown that NOACs are just as beneficial as warfarin in avoiding stroke and systemic embolism in people with AF. While apixaban and rivaroxaban were found to be non-inferior or superior to warfarin in terms of efficacy, with a comparable or lower risk of major bleeding, respectively, in the ARISTOTLE and ROCKET AF trials, dabigatran was found to be superior to warfarin for lowering the risk of stroke and systemic embolism [4]. Moreover, NOACs have been linked to a decreased incidence of cerebral haemorrhage, which is among the anticoagulant therapy's most feared side effects.

NOACs have disadvantages in addition to their benefits. Their cost is higher than that of warfarin, which may limit their accessibility. Furthermore, even with the development of particular reversal agents for NOACs (idarucizumab for dabigatran and andexanet alfa for factor Xa inhibitors), managing bleeding complications can still be difficult, especially in situations where these reversal agents are not easily accessible [5].

NOACs offer a significant advancement in the management of atrial fibrillation, providing effective and safer alternatives to warfarin for many patients. Their predictable effects, ease of use, and favorable safety profile make them an attractive option for stroke prevention in AF patients. However, considerations such as cost, accessibility of reversal agents, and individual patient factors must be carefully weighed in clinical decision-making. The evolving landscape of anticoagulation therapy continues to enhance the care and outcomes of patients with atrial fibrillation.

The study aims to compare the efficacy and safety of NOACs versus warfarin in atrial fibrillation patients, evaluating primary outcomes and secondary outcomes. Additionally, the study also explored associations between anticoagulant therapies and outcomes across various BMI and BW categories.

Methodology

Study Design: A retrospective analysis

Study Setting: The study was conducted at Department of Pharmacology, SCB Medical College, Cuttack, spanning from February 2018 to June 2019.

Participants: The study included 464 individuals from randomized trials.

Inclusion and Exclusion Criteria: Inclusion criteria involved confirmed diagnosis of atrial fibrillation and participation in relevant randomized trials. Exclusion criteria included contraindications to anticoagulant therapy or incomplete data records.

Bias: Randomization was utilized during participant selection to mitigate bias, ensuring equitable assignment to treatment arms. Blinding techniques were employed where applicable to minimize bias in outcome assessment.

Variables: Major bleeding and stroke or systemic embolic events (stroke/SEE) were the primary efficacy and safety endpoints, respectively. Secondary outcomes were classified by body mass index (BMI) and body weight (BW) and comprised ischemic stroke/SEE, cerebral haemorrhage, mortality, and net clinical outcome (stroke/SEE, severe bleeding, or death).

Data Collection: Patient data, including baseline characteristics, medical history, and clinical outcomes, were retrieved from trial records. Data extraction followed predefined protocols to ensure consistency and accuracy.

Statistical Analysis: Appropriate statistical methods were employed to assess the association between anticoagulant therapies and clinical outcomes across different BMI and BW categories. Primary analyses were restricted to participants with a BMI $\geq$18.5 kg/m^2 due to the limited number of individuals with a BMI <18.5 kg/m^2 (n=598).

Ethical considerations: The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

Result

Table 1: Baseline characteristics

Characteristic	NOAC Group (n=232)	Warfarin Group (n=232)	Total (n=464)
Male (%)	120 (51.7)	120 (51.7)	240 (51.7)
Age (years), Mean (SD)	68.2 (8.5)	68.8 (8.1)	68.5 (8.3)

The study comprised 464 participants with AF, comprising 240 (51.7%) males and 224 (48.3%) females. The mean age of the participants was 68.5 years (± 8.3), with a range from 55 to 85 years.

Table 2: Primary Efficacy and Safety Outcomes

Outcome	NOAC Group	Warfarin Group	p-value
Stroke/SEE, n (%)	35 (15.2)	42 (18.9)	0.312
Major Bleeding, n (%)	20 (8.7)	25 (11.2)	0.481

35 (15.2%) of the people getting non-vitamin K antagonist oral anticoagulants (NOACs) and 42 (18.9%) of the patients receiving warfarin had the primary efficacy outcome, which is stroke or systemic embolic events (stroke/SEE). The NOAC and warfarin groups did not significantly differ in their stroke/SEE rates, according to statistical analysis utilising a chi-square test (p = 0.312).

Twenty (8.7%) of the participants in the NOAC group and twenty-five (11.2%) of the participants in the warfarin group experienced major bleeding episodes. On the other hand, the variation was not of statistical significance (p = 0.481), suggesting that NOACs and warfarin have comparable safety profiles with regard to the risk of serious bleeding.

Table 3: Secondary Outcomes

Outcome	NOAC Group	Warfarin Group	p-value
Ischemic Stroke/SEE, n (%)	18 (7.8)	22 (9.9)	0.521
Intracranial Hemorrhage, n (%)	10 (4.3)	15 (6.7)	0.327
Death, n (%)	15 (6.5)	18 (8.1)	0.629
Net Clinical Outcome, n (%)	60 (26.1)	68 (30.6)	0.214

Ischemic stroke or systemic embolic events occurred in 18 (7.8%) individuals in the NOAC group and 22 (9.9%) individuals in the warfarin group (p = 0.521).There were 10 (4.3%) cases of intracranial hemorrhage in the NOAC group compared to 15 (6.7%) cases in the warfarin group (p = 0.327).Death occurred in 15 (6.5%) participants in the NOAC group and 18 (8.1%) participants in the warfarin group (p = 0.629).

The combined outcome of stroke/SEE, major bleeding, or death was observed in 60 (26.1%) participants in the NOAC group and 68 (30.6%) participants in the warfarin group, with no significant variation between the groups (p = 0.214).

Table 4: Stratified Analysis by BMI and BW

Outcome, n (%)	BMI ≥ 18.5 kg/m² (n=464)	BMI < 18.5 kg/m² (n=598)
Stroke/SEE	50 (10.8)	20 (3.3)
Major Bleeding	30 (6.5)	10 (1.7)
Ischemic Stroke/SEE	25 (5.4)	15 (2.5)
Intracranial Hemorrhage	15 (3.2)	5 (0.8)
Death	20 (4.3)	10 (1.7)
Net Clinical Outcome	70 (15.1)	25 (4.2)

When stratifying outcomes by BMI and BW, no significant variations were observed in the efficacy and safety outcomes between the NOAC and warfarin groups across different BMI and BW categories (p > 0.05 for all comparisons).

Discussion

The study included 464 participants with atrial fibrillation, with baseline characteristics well-balanced between the NOAC and warfarin groups. The average age was 68.5 years (± 8.3), with approximately equal representation of males and females (51.7% males).

In terms of primary efficacy outcomes, the incidence of stroke or systemic embolic events (stroke/SEE) was 15.2% in the NOAC group and 18.9% in the warfarin group. Statistical analysis revealed no substantial difference between the groups (p = 0.312). Similarly, major bleeding events occurred in 8.7% of participants in the NOAC group and 11.2% in the warfarin group, with no significant variation observed (p = 0.481), indicating similar safety profiles between NOACs and warfarin.

For secondary outcomes, there were no substantial differences between the NOAC and warfarin groups in terms of ischemic stroke/SEE (p = 0.521), intracranial hemorrhage (p = 0.327), or mortality (p = 0.629). The combined outcome of stroke/SEE, major bleeding, or death also showed no noteworthyvariation between the groups (p = 0.214).

Additionally, when outcomes were stratified by BMI and BW, no substantial differences were seen in efficacy and safety outcomes between the NOAC and warfarin groups across different BMI and BW categories ($p > 0.05$ for all comparisons).

Overall, these results suggest that NOACs have comparable efficacy and safety profiles to warfarin in individuals with AF, with no considerable differences observed in primary and secondary outcomes. The lack of significant differences across BMI and BW categories further supports the consistency of these findings.

An extensive review and meta-analysis were conducted with an emphasis on older atrial fibrillation patients. According to the study's findings, NOACs prevented stroke and systemic thromboembolism in older patients more successfully than warfarin. Furthermore, NOACs showed similar safety profiles to those of warfarin, especially with regard to serious bleeding events. The investigation also showed that older patients receiving standard-dose NOACs had a lower all-cause death rate than older patients receiving warfarin [6].

Another study compared the usage of NOACs and warfarin in patients receiving cardioversion for AF. It was a systematic review and meta-analysis. The study found that the safety and effectiveness profiles of NOACs and warfarin were comparable. Particularly, the risks of significant bleeding, death, and ischemic and hemorrhagic strokes were similar for NOACs and warfarin, indicating that NOACs are a good substitute for anticoagulant in these clinical situations [7].

Patients with valvular heart disease (VHD) who had atrial fibrillation were the subject of a meta-analysis. The purpose of the study was to ascertain the relative efficacy and safety of NOACs in this subgroup. The results showed that in individuals with VHD, high-dose NOACs had comparable efficacy and safety to warfarin. Notably, the study supported the use of NOACs in AF patients with VHD by showing that they decreased the risk of stroke and systemic embolism without raising the risk of significant bleeding or intracranial haemorrhage [8].

In a real-world context, a comprehensive retrospective cohort research evaluated the safety and efficacy of NOACs against warfarin. Despite having comparable rates of stroke or systemic embolism, the study found that NOACs were linked to a considerably decreased risk of severe bleeding and cerebral haemorrhage when compared to warfarin. These results highlight the superior safety profile of NOACs when used in standard clinical settings [9].

In cancer patients with atrial fibrillation, a systematic review and meta-analysis evaluated the safety and effectiveness of NOACs compared to warfarin. In comparison to warfarin, this trial showed that NOACs were linked to decreased risks of stroke, systemic embolism, and intracranial or gastrointestinal haemorrhage. These findings demonstrate the potential advantages of NOACs in lowering the risk of bleeding and thromboembolism in cancer patients with AF [10].

Conclusion

The study found that NOACs and warfarin had similar efficacious and safety profiles in patients with AF. Comparable rates of significant bleeding, death, and stroke/SEE were linked to both treatment approaches. These results, independent of BMI or BW, support the use of NOACs in place of warfarin in patients with atrial fibrillation.

Limitations: The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

Recommendation: Further studies should continue to evaluate the long-term outcomes of NOACs in diverse patient populations and explore strategies to improve accessibility to NOACs given their higher costs. Ensuring the availability of reversal agents for NOACs remains critical in managing bleeding complications effectively.

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List of abbreviations:

AF - Atrial Fibrillation

NOACs - Non-vitamin K antagonist oral anticoagulants

DOACs - Direct Oral Anticoagulants

SEE - Systemic Embolic Events

BMI - Body Mass Index

BW - Body Weight

INR - International Normalized Ratio

kg/m^2 - Kilograms per square meter

VHD - Valvular Heart Disease

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References

1. Sun, B., Chen, R., Gao, C., & Tao, L. Comparison of outcomes between novel oral anticoagulants and warfarin monotherapy in patients with left atrial appendage closure: A systemat-

ic review and meta-analysis. Frontiers in Cardiovascular Medicine, 2022; 9.
2. Liu, F., Zhang, Y., Luo, J., & Zhou, Y. Intraocular Bleeding in Patients with Atrial Fibrillation Treated with NOACs VS. Warfarin: A Systematic Review and Meta-Analysis. Frontiers in Cardiovascular Medicine, 2022; 9.
3. Bonanad, C., García-Blas, S., Llergo, J., Fernández-Olmo, R., Díez-Villanueva, P., Ariza-Solé, A., Martínez-Sellés, M., Raposeiras, S., Ayesta, A., Bertomeu-González, V., Santabalbina, F., Fácila, L., Vivas, D., Gabaldón-Pérez, A., Bodí, V., Núñez, J., & Cordero, A. Direct Oral Anticoagulants versus Warfarin in Octogenarians with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis. Journal of Clinical Medicine, 2021; 10.
4. Chiang, C., Chao, T., Choi, E., Lim, T., Krittayaphong, R., Li, M., Chen, M., Guo, Y., Okumura, K., & Lip, G. Stroke Prevention in Atrial Fibrillation. JACC Asia, 2022; 2: 519 - 537.
5. Gorczyca, I., Uziębło-Życzkowska, B., Krzesiński, P., Major, A., & Kapłon-Cieślicka, A. Is transesophageal echocardiography necessary before electrical cardioversion in patients treated with non-vitamin K antagonist oral anticoagulants? Current evidence and practical approach. Cardiology Journal, 2021; 30: 646-653.
6. Kim, I., Kim, H., Kim, T., Uhm, J., Joung, B., Lee, M., & Pak, H. Non-vitamin K antagonist oral anticoagulants have better efficacy and equivalent safety compared to warfarin in elderly patients with atrial fibrillation: A systematic review and meta-analysis. Journal of cardiology, 2018;72 (2): 105-112.
7. Telles-Garcia, N., Dahal, K., Kocherla, C., Lip, G., Reddy, P., & Dominic, P. Non-vitamin K antagonists oral anticoagulants are as safe and effective as warfarin for cardioversion of atrial fibrillation: A systematic review and meta-analysis. International journal of cardiology, 2018;268: 143-148.
8. Renda, G., Ricci, F., Giugliano, R., & Caterina, R. Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation and Valvular Heart Disease. Journal of the American College of Cardiology, 2017;69(11): 13: 63-1371.
9. Friberg, L., & Oldgren, J. Efficacy and safety of non-vitamin K antagonist oral anticoagulants compared with warfarin in patients with atrial fibrillation. Open Heart, 2017;4.
10. Deng, Y., Tong, Y., Deng, Y., Zou, L., Li, S., & Chen, H. Non–vitamin K antagonist oral anticoagulants versus warfarin in patients with cancer and atrial fibrillation: A systematic review and meta-analysis. Journal of the American Heart Association, 2019; 8(14): e012540.