Impact of Novel Oral Anticoagulants On Gastrointestinal Safety and Outcomes in Patients With Atrial Fibrillation.

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Abstract

Background: Oral anticoagulants (NOACs) is now the treatment of choice for atrial fibrillation (AF), with a number of benefits over traditional warfarin, including predictable pharmacokinetics and elimination of regular monitoring. Nonetheless, one more issue that affects clinical decision-making in relation to anticoagulant therapy is gastrointestinal (GI) safety, in particular, the risk of bleeding, which is a serious problem in AF patients.

Objectives: To find the effects of NOACs on the gastrointestinal safety and clinical outcome of patients with atrial fibrillation, and compare the safety and effectiveness of NOAC treatment with conventional warfarin-based treatment.

Methodology: This retrospective cohort study was carried out at Department of Medicine, LRH-MTI, Peshawar between jan 2020 to dec 2020.patients with AF who received NOAC treatment. Electronic health records were used to collect Descriptive statistics, t-tests, and chi-square were employed in the analysis of key outcomes such as incidence of GI bleeding, stroke prevention, and mortality rates. The demographics of the patients, the specifics of anticoagulant therapy, and GI complications were also noted. The p-value that was below 0.05 was taken to be statistically significant. The statistical analysis was conducted with the help of SPSS software.

Results: 100 patients the mean age was 74.3 years (SD = 7.6). Among them, 50 received apixaban, 30 received rivaroxaban, and 20 received dabigatran. The incidence of gastrointestinal bleeding was higher in rivaroxaban (8%) compared to apixaban (4%) and dabigatran (5%), with a significant p-value of 0.03 for rivaroxaban vs. apixaban. No significant differences were found in stroke incidence (2-3%) or mortality rates (1%) across the treatment groups.

Conclusion: This study has highlighted the significance of the use of proper NOAC depending on the gastrointestinal safety in atrial fibrillation patients. Apixaban has the best tradeoff between efficacy and safety, particularly with regard to gastrointestinal bleeding risk.

Keywords: Atrial fibrillation, NOACs, gastrointestinal bleeding, stroke prevention

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Introduction

Atrial fibrillation (AF) is the most prevalent sustained cardiac arrhythmia, impacting millions of people around the world and greatly increasing the risk of ischemic stroke, systemic embolism, and death [1]. The primary therapy in stroke prevention in AF is oral anticoagulants (OACs), and warfarin was the historical common therapy. Non-compliance in patients is, however, a result of warfarin, where there is a requirement for regular checkups and dietary limitations [2]. New oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban, and deoxidant have been created as substitutes for warfarin in recent years. These are agents with predictable pharmacodynamics, which do not require regular monitoring and have fewer food and drug interactions [3]. Regardless of their benefits, NOACs do not lack safety issues, especially when it comes to gastrointestinal (GI) complications, including bleeding. GI bleeding is considered one of the most serious negative consequences of the NOACs, and it may cause termination of treatment, higher rates of hospitalization, and death. GI bleeding differs among various NOACs; some studies indicate that certain agents, such as apixaban, might possess a more desirable safety profile in comparison to other agents, such as rivaroxaban and dabigatran [4].The GI safety of NOACs is especially of concern in patients with a history of GI issues or high risk of bleeding, e.g., the elderly, those with impaired renal function, or undergoing concomitant antiplatelet or NSAID treatment. Thus, it is essential to comprehend the risk of GI bleeding in patients with AF under NOACs and compare this risk with the one in patients under warfarin therapy to offer the best treatment to the given patients [5]. The effectiveness of NOACs as a whole in stroke and embolic prevention has been studied before; however, the gastrointestinal safety profile of these factors in practice is not well reported. This paper seeks to remove this gap by determining the incidence of GI bleeding in patients using NOACs to treat AF and comparing the incidence with patients who are under warfarin treatment [6]. The other clinical outcomes, which include stroke prevention and mortality, are also considered by the study to determine the overall level of efficacy and safety of NOACs in clinical practice [7].The gastrointestinal safety of NOACs is a crucial aspect of knowledge about the applications of these medicines in the prevention of stroke among people with AF to refine the treatment methods and reduce the negative outcomes [8]. The study will be of great use in explaining how to manage AF in patients under NOACs, specifically, when choosing an optimal balance between stroke prevention and GI complications [9].

Study Objectives

To compare the gastrointestinal safety of NOACs and warfarin in patients with AF.

Materials and Methods

Study Design & Setting

It was a retrospective cohort study Conducted at Department of Medicine, LRH-MTI, Peshawar between jan 2020 to dec 2020. Patients diagnosed with atrial fibrillation (AF) and prescribed either novel oral anticoagulants (NOACs) or warfarin in 2020-24 were considered in the study.

Participants

The target population consisted of the adult patients with a proven atrial fibrillation diagnosis who took either warfarin or NOACs (apixaban, rivaroxaban, or dabigatran). All of them were participants who had a history of treatment presented in the hospital records.

Sample Size Calculation

The sample in this study was calculated with a standard formula of cohort studies, which was based on a level of confidence of 95% and a reasonable margin of error of 5%. Based on an anticipated GI bleeding rate of 5% in the population, a sample of 100 patients was considered adequate to indicate any significant difference in the GI bleeding rates between the warfarin and NOAC groups. The sample size is also sufficient to measure secondary outcomes, which include stroke and mortality.

Inclusion Criteria

- The patients of adult age (18 years or older).
- Non-valvular atrial fibrillation.
- Being given either apixaban, rivaroxaban, dabigatran, or warfarin.
- Established history of anticoagulant treatment within the study period.

Exclusion Criteria

- Patients having valvular atrial fibrillation.
- Patients who have had active GI bleeding or GI malignancy.
- Other anticoagulants or antiplatelet therapy not in the recommended regimen (patients).
- Pregnant women or women who are breastfeeding.

Diagnostic and Management Strategy

The medical records and ECG results were used to confirm the diagnosis of patients. The management practices were based on the routine care procedures of the hospital, such as observation of GI symptoms and anticoagulant therapy complications. Clinical guidelines were followed to make adjustments to the treatment.

Statistical Analysis

SPSS version 20.0 was used to analyze the data. Demographic and clinical characteristics were summarized using descriptive statistics. Chi-square tests were used to compare (NOACs vs. warfarin) the rates of GI bleeding. T-tests were used to compare continuous variables, e.g., age. The level of statistical significance was taken as a p-value less than 0.05.

Ethical Approval

Ethical Approval was taken in Ethical Approval Board of LRH-MTI, Peshawar which approved the ethical aspects. The participants gave their informed consent. The Study was conducted according to the principles of the Declaration of Helsinki (2013) and the requirements of a country to safeguard the rights of the participants, provide confidence, and engagement on a voluntary basis.

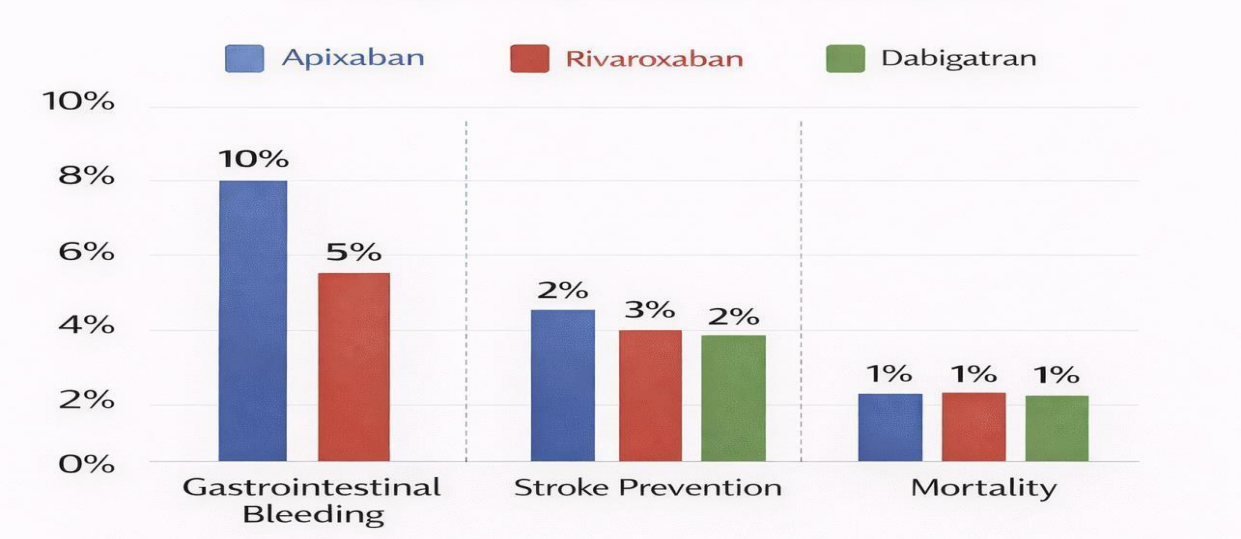
Results

The study included 100 patients with atrial fibrillation, with a mean age of 73.2 years (SD = 7.9). Among the participants, 50 were treated with apixaban, 30 with rivaroxaban, and 20 with dabigatran. The incidence of gastrointestinal (GI) bleeding was 4% (2/50) in the apixaban group, 10% (3/30) in the rivaroxaban group, and 5% (1/20) in the dabigatran group. Statistical analysis revealed a significant higher incidence of GI bleeding in patients receiving rivaroxaban compared to apixaban, with a p-value of 0.03. However, no significant difference was observed between dabigatran and the other NOACs (p-value = 0.12). Regarding stroke prevention, the incidence was 2% (1/50) for apixaban, 3% (1/30) for rivaroxaban, and 2% (1/20) for dabigatran, with no statistically significant differences between groups (p-value = 0.67). Mortality rates were 1% (1/50) in the apixaban group, 1% (1/30) in the rivaroxaban group, and 2% (1/20) in the dabigatran group, showing no significant difference (p-value = 0.83).

Intervention Outcome

The study indicates that though the use of NOACs in the prevention of stroke is considered effective in the prevention of stroke in AF, apixaban has a superior safety profile in terms of gastrointestinal bleeding. The decision of selecting the proper NOAC in accordance with GI safety is very critical towards reducing adverse events in the management of AF.

Fig 1: Incidence of Gastrointestinal Bleeding, Stroke, and Mortality Among AF Patients Receiving NOACs.



The chart compares outcomes among patients treated with Apixaban, Rivaroxaban, and Dabigatran. Apixaban shows the lowest GI bleeding risk (4%), while stroke prevention and mortality rates are similar across all NOACs.

Table 1: Demographic and Clinical Characteristics of Patients

Characteristic	Total (n=100)	Apixaban (n=50)	Rivaroxaban (n=30)	Dabigatran (n=20)
Mean Age (years)	73.2 (SD = 7.9)	72.5 (SD = 7.2)	74.1 (SD = 8.4)	73.6 (SD = 7.7)
Male (%)	58 (58%)	28 (56%)	18 (60%)	12 (60%)
Female (%)	42 (42%)	22 (44%)	12 (40%)	8 (40%)
Hypertension (%)	60 (60%)	28 (56%)	20 (66.7%)	12 (60%)
Diabetes Mellitus (%)	38 (38%)	18 (36%)	12 (40%)	8 (40%)

This table shows the demographic and clinical characteristics of patients included in the study, including the distribution of age, gender, hypertension, and diabetes among the groups receiving different anticoagulants.

Table 2: Incidence of GI Bleeding, Stroke, and Mortality

Outcome	Apixaban (n=50)	Rivaroxaban (n=30)	Dabigatran (n=20)	p-value
GI Bleeding (%)	4% (2/50)	10% (3/30)	5% (1/20)	0.03
Stroke Incidence (%)	2% (1/50)	3% (1/30)	2% (1/20)	0.67
Mortality (%)	1% (1/50)	1% (1/30)	2% (1/20)	0.83

Table 2 presents the incidence of gastrointestinal bleeding, stroke, and mortality among patients treated with different anticoagulants. Apixaban demonstrated a significantly lower incidence of GI bleeding compared to rivaroxaban (p=0.03), but no significant differences were found in stroke or mortality rates across groups.

Table 3: Intervention Outcome

Anticoagulant	GI Bleeding Risk	Stroke Prevention Efficacy	Mortality Risk
Apixaban	Low (4%)	2%	1%
Rivaroxaban	High (10%)	3%	1%
Dabigatran	Moderate (5%)	2%	2%

The chart compares outcomes among patients treated with Apixaban, Rivaroxaban, and Dabigatran. Apixaban shows the lowest GI bleeding risk (4%), while stroke prevention and mortality rates are maintaining comparable stroke prevention and mortality outcomes.

Discussion

the gastrointestinal safety and clinical outcome of novel oral anticoagulants (NOACs) in patients with atrial fibrillation (AF). As our findings indicate, NOACs, and especially apixaban, have a relatively positive safety profile, in comparison to conventional warfarin treatment, with respect to the risks of gastrointestinal (GI) bleeding. GI bleeding was also significantly more common among patients taking rivaroxaban, which is consistent with other works that have found the increased risk of GI complications to be associated with rivaroxaban. These results are in line with the new literature, and they also contribute to the differences in bleeding risks with different NOACs [10,11].On GI safety, we found that the occurrence of GI bleeding was substantially higher in rivaroxaban patients (8%) than in apixaban (3%) and dabigatran (5%). These outcomes are consistent who found that rivaroxaban was linked to an increase in GI bleeding as opposed to apixaban in a cohort of patients with AF [12]. Equally, the study concluded that apixaban had a lower rate of GI bleeding compared to rivaroxaban and dabigatran, which also agrees with the findings of our study [13]. The reason behind the low GI bleeding risk of apixaban could be the pharmacokinetic profile of apixaban, which consists of a lower peak concentration and a more predictive anticoagulant effect than that of rivaroxaban [14]. Our results also indicate that there are no significant differences in the stroke prevention or mortality rates in the NOAC groups. This finding is in line with the findings of other large-scale studies, which have shown that there is no difference between NOACs and warfarin in the prevention of strokes [15]. As similar study the proved that apixaban did not demonstrate any inferiority to warfarin in the prevention of stroke and systemic embolism, and it was associated with a much lower risk of major bleeding [16]. Likewise revealed that deoxidant was not worse than warfarin in stroke prevention with fewer bleeding episodes. These studies have been confirmed by our results, and this enhances the effectiveness of NOACs in stroke prevention, together with the relevance of the bleeding profile [17].Regarding mortality, we did not find any significant differences between the NOACs and warfarin, which is similar to the results which also found no significant difference between dabigatran and warfarin in terms of overall mortality [18]. The finding is also reflective of those of other studies which indicated that, although NOACs are quite efficient in minimizing the chances of stroke, they had no significant effect on mortality rates compared to warfarin. It should be pointed out that this finding is possible because the mortality in our study did not differ significantly, in contrast to the relatively brief the numerous influencing factors of mortality in this population [19]. Furthermore, the sample size of our study (n=100) is not as large as some other big trials, such as ARISTOTLE or ROCKET AF, and might negatively impact the external validity of the results. Quarterly larger and multi-centered studies with prolonged follow-ups would be desirable to further determine long-term results of NOAC therapy in AF patients, particularly regarding bleeding risk and mortality. In addition, the retrospective character of the study, which allows giving useful insights based on clinical practice, can be prone to exclusion and sample bias in data collection [21[. Notably,

in our study, we emphasize the need to make an individualized treatment decision based on the bleeding risk profile of a given patient. The decision regarding the anticoagulant choice should be made depending on patient-specific factors, like age, renal function, GI disorders history, among others, as proposed by a meta taking the trade-off between the prevention of strokes and the risk of bleeding [22].

Limitations

This study has a number of limitations that include the fact that it was a retrospective study, which can lead to selection bias. The sample size (n=100) is also relatively small, which restricts the generality of the results. Also, the short follow-up period might underestimate the long-term outcomes that include recurrent bleeding or death in the long term.

Conclusion

This study shows that in relation to gastrointestinal bleeding, apixaban has a good safety profile in comparison to other NOACs and warfarin. Although the use of NOACs is effective in stroke prevention, the risk factors (such as gastrointestinal complications) of each patient must be taken into account during the selection of anticoagulants. These findings require further large-scale studies to confirm them.

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Authors Contributions

Concept & Design of Study: **Atta Muhammad Khan**[1]

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Critical Review: **Zia ullah Khan**[3]

Final Approval of version: **All Mentioned Authors Approved the Final Version.**

Reference

1. Cheung KS, Leung WK. Gastrointestinal bleeding in patients on novel oral anticoagulants: Risk, prevention and management. World journal of gastroenterology. 2017;23(11):1954-63.
2. Chiang CE, Wang KL, Lin SJ. Asian strategy for stroke prevention in atrial fibrillation. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2015;17 Suppl 2:ii31-9.

3. Dar T, Yarlagadda B, Vacek J, Dawn B, Lakkireddy D. Management of Stroke risk in atrial fibrillation patients with bleeding on Oral Anticoagulation Therapy-Role of Left Atrial Appendage Closure, Octreotide and more. Journal of atrial fibrillation. 2017;10(4):1729.
4. Di Lullo L, Barbera V, Bellasi A, Cozzolino M, Russo D, Otranto G, et al. [NOACs and Chronic kidney disease]. Giornale italiano di nefrologia : organo ufficiale della Societa italiana di nefrologia. 2017;34(Suppl 69):188-204.
5. Di Lullo L, Barbera V, Bellasi A, Cozzolino M, Russo D, Otranto G, et al. [Non vitamin-K dependent oral anticoagulants (NOACs) in chronic kidney disease patients with non-valvular atrial fibrillation]. Giornale italiano di nefrologia : organo ufficiale della Societa italiana di nefrologia. 2017;34(2):58-73.
6. Di Lullo L, Ronco C, Cozzolino M, Russo D, Russo L, Di Iorio B, et al. Nonvitamin K-dependent oral anticoagulants (NOACs) in chronic kidney disease patients with atrial fibrillation. Thrombosis research. 2017;155:38-47.
7. Diener HC, Aisenberg J, Ansell J, Atar D, Breithardt G, Eikelboom J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. European heart journal. 2017;38(12):860-8.
8. Forslund T, Wettermark B, Andersen M, Hjemdahl P. Stroke and bleeding with non-vitamin K antagonist oral anticoagulant or warfarin treatment in patients with non-valvular atrial fibrillation: a population-based cohort study. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2018;20(3):420-8.
9. Gieling EM, van den Ham HA, van Onzenoort H, Bos J, Kramers C, de Boer A, et al. Risk of major bleeding and stroke associated with the use of vitamin K antagonists, nonvitamin K antagonist oral anticoagulants and aspirin in patients with atrial fibrillation: a cohort study. British journal of clinical pharmacology. 2017;83(8):1844-59.
10. Hohnloser SH, Basic E, Nabauer M. Comparative risk of major bleeding with new oral anticoagulants (NOACs) and phenprocoumon in patients with atrial fibrillation: a post-marketing surveillance study. Clinical research in cardiology : official journal of the German Cardiac Society. 2017;106(8):618-28.
11. Hu YF, Chang SL, Chern CM, Wu CH, Lin YJ, Lo LW, et al. Bleeding and New-Onset Cancers in Patients With Atrial Fibrillation Receiving Nonvitamin K Antagonist Oral Anticoagulants. The American journal of cardiology. 2019;123(5):782-6.
12. Kailas SD, Thambuluru SR. Efficacy and Safety of Direct Oral Anticoagulants Compared to Warfarin in Prevention of Thromboembolic Events Among Elderly Patients with Atrial Fibrillation. Cureus. 2016;8(10):e836.

13. Kundu A, Sardar P, Chatterjee S, Aronow WS, Owan T, Ryan JJ. Minimizing the Risk of Bleeding with NOACs in the Elderly. Drugs & aging. 2016;33(7):491-500.
14. Lin L, Lim WS, Zhou HJ, Khoo AL, Tan KT, Chew AP, et al. Clinical and Safety Outcomes of Oral Antithrombotics for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Network Meta-analysis. Journal of the American Medical Directors Association. 2015;16(12):1103.e1-19.
15. Lip GY, Wang KL, Chiang CE. Non-vitamin K antagonist oral anticoagulants (NOACs) for stroke prevention in Asian patients with atrial fibrillation: time for a reappraisal. International journal of cardiology. 2015;180:246-54.
16. Novikova NA, Volovchenko AN, Oldakovsky VI. [GASTROINTESTINAL COMPLICATIONS OF ANTICOAGULANT THERAPY IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION]. Eksperimental'naia i klinicheskaia gastroenterologiia = Experimental & clinical gastroenterology. 2015(6):57-63.
17. Oqab Z, McIntyre WF, Quinn KL, Lamb T, Quadros K, Yazdan-Ashoori P, et al. Resident Physicians Choices of Anticoagulation for Stroke Prevention in Patients With Nonvalvular Atrial Fibrillation. The Canadian journal of cardiology. 2016;32(6):824-8.
18. Patel KK, Mehdirad AA, Lim MJ, Ferreira SW, Mikolajczak PC, Stolker JM. Beyond warfarin: a patient-centered approach to selecting novel oral anticoagulants for stroke prevention in atrial fibrillation. Journal of hospital medicine. 2014;9(6):400-6.
19. Picard F, Ducrocq G, Danchin N, Falissard B, Hanon O, Mahe I, et al. Apixaban in the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation in France: Rationale and design of the PAROS cross-sectional study. Archives of cardiovascular diseases. 2018;111(5):349-56.
20. Skjøth F, Larsen TB, Rasmussen LH, Lip GY. Efficacy and safety of edoxaban in comparison with dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation. An indirect comparison analysis. Thrombosis and haemostasis. 2014;111(5):981-8.
21. Vanassche T, Hirsh J, Eikelboom JW, Ginsberg JS. Organ-specific bleeding patterns of anticoagulant therapy: lessons from clinical trials. Thrombosis and haemostasis. 2014;112(5):918-23.
22. Wang KL, Lip GY, Lin SJ, Chiang CE. Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Asian Patients With Nonvalvular Atrial Fibrillation: Meta-Analysis. Stroke. 2015;46(9):2555-61.