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PATIENT ADHERENCE TO NOAC THERAPY IN ATRIAL FIBRILLATION AND ITS IMPACT ON CLINICAL OUTCOMES: A NARRATIVE REVIEW

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ABSTRACT

BACKGROUND

Atrial fibrillation is one of the most common sustained cardiac arrhythmias and is associated with a high risk of ischemic stroke, thromboembolic complications, and mortality. Direct oral anticoagulants are widely used for stroke prevention in patients with atrial fibrillation and are currently considered standard therapy. However, the effectiveness of this therapy largely depends on long term patient adherence and persistence with treatment, since missed doses or premature discontinuation reduce the level of anticoagulant protection.

AIMS

The aim of this review was to summarize current evidence on adherence and persistence to direct oral anticoagulant therapy in atrial fibrillation, to compare these indicators between individual agents, and to analyze factors influencing treatment adherence and associated clinical outcomes.

METHODS

The study was conducted as a narrative literature review. Publications were searched in the PubMed and Google Scholar databases. Studies published between 2015 and 2025 were considered. Titles and abstracts were screened followed by full text assessment of potentially relevant studies. A total of 57 publications addressing treatment adherence, persistence, dosing practices, and clinical outcomes of direct oral anticoagulants in patients with atrial fibrillation were analyzed. Due to substantial heterogeneity of study designs and outcome measures, a qualitative synthesis of the evidence was performed without quantitative meta analysis. The comparative analysis focused on rivaroxaban, dabigatran, and apixaban. Edoxaban was not analyzed separately because of limited and heterogeneous data in the available studies.

RESULTS

Analysis of published observational studies demonstrates substantial variability in adherence and treatment persistence among different direct oral anticoagulants. In most cohort studies higher adherence is observed with rivaroxaban and apixaban compared with dabigatran. Several studies also report longer treatment persistence with apixaban during long term follow up. These differences are partly explained by dosing regimens, treatment tolerability, and the frequency of adverse effects. Incorrect dosing of anticoagulants represents a common problem in clinical practice and is observed in a considerable proportion of patients, with underdosing occurring more frequently than overdosing. Deviations from recommended dosing regimens are associated with poorer clinical outcomes, including increased risk of thromboembolic complications. Treatment adherence is also influenced by multiple factors such as patient age, polypharmacy, complexity of dosing regimens, and socioeconomic conditions of medical care.

CONCLUSIONS

Adherence and persistence to direct oral anticoagulant therapy in patients with atrial fibrillation differ substantially between individual drugs and patient populations. Lower adherence is more frequently observed with dabigatran, whereas factor Xa inhibitors, particularly rivaroxaban and apixaban, demonstrate higher levels of treatment adherence in most studies. Incorrect dosing and clinical factors affecting treatment continuation represent important determinants of anticoagulant therapy effectiveness. Optimization of therapy requires individualized drug selection, appropriate dose adjustment according to renal function and clinical guidelines, and the implementation of strategies aimed at improving long term adherence to anticoagulant therapy.

Keywords: NOAC, adherence, persistence, atrial fibrillation, anticoagulant therapy, stroke prevention

INTRODUCTION

Atrial fibrillation (AF) is the most frequent sustained cardiac arrhythmia in the USA and Europe.[1-2] In 2016, the global prevalence of AF was estimated to be approximately 46.3 million people, reflecting a threefold increase over the past 50 years.[3] AF symptoms are highly variable and can include palpitations, dyspnea, chest pain, anxiety, depression, reduced exercise tolerance, polyuria, and fatigue, however up to one-third of patients may be asymptomatic.[4]

AF raises the risk of dementia, Alzheimer's disease, vascular dementia, ventricular arrhythmias, major adverse cardiovascular events (MACE), heart failure,[5-7] and crucially, the risk of ischemic stroke by approximately three to five times, and it is responsible for up to 15% of strokes across all age groups.[8]

The remarkable rising incidence, prevalence, high lifetime risk, and leading to other above-mentioned sequelae, make AF a relevant illness in the population with high morbidity, mortality, and significant health care costs.[3]

Nowadays, the best way to prevent stroke in people with AF is antithrombotic therapy, specifically novel anticoagulants (NOAC). In comparison to vitamin K antagonists (VKA), which have served as the primary method for stroke prevention in patients with AF for many years, NOAC provide similar or greater effectiveness and safety compared to VKA for preventing strokes in individuals with non-valvular atrial fibrillation.[9]

They offer benefits such as coherent dosing, more consistent pharmacokinetic profile, less interactions with other drugs and no requirement for regular international normalized ratio (INR) monitoring, which improves patient adherence and compliance of treatment.[10]

Based on the literature, adherence refers to a patient’s active decision to follow a prescribed treatment plan while taking responsibility for their own health. In contrast, compliance is viewed as a more passive act, where the patient follows the doctor’s instructions without necessarily engaging in the decision-making process. Adherence in medical therapy is preferable, as it is considered a more constructive and intentional behavior, often involving long-term lifestyle changes[11] and better persistence, which refers to how long a patient continues taking their prescribed treatment from the start until they stop.[12]

The most frequently used adherence measures are medication possession ratio (MPR) and proportion of days covered (PDC). MPR is calculated by dividing the total days of medication supply between the initial prescription claim and the final prescription claim during the follow-up period by the total number of days in that period. The follow-up duration for the denominator varies and is based on the number of days between the index date and the last dispensed prescription, including supply days. PDC is determined as the total number of days within the follow-up period in which medication was available (excluding overlapping supply days) divided by the length of the observation period. [13] In most of the studies, adherence is defined as PDC >0,8 (or 80%).[14-16]

According to research, there are many factors that can affect compliance, adherence and persistence in medical

therapy. For example, Qureshi and Wassan (2024) study has shown that in diabetic patients factors such as monthly income, hypoglycemic episodes, attitudes, gender, misconceptions, and insufficient education about the disease can affect compliance and adherence.[17]

Washington and Langdon (2021) study shows that in patients with multiple sclerosis diagnosis of depression or the presence of at least one psychiatric disorder was linked to decreased adherence. Besides, alcohol use (frequency and amount) was linked to a higher likelihood of missing one or several doses. Also self-reported memory problems or forgetfulness were connected to decreased adherence and a higher likelihood of missing doses. Finally, patients who were well informed about their condition and treatment demonstrated significantly better adherence.[18]

Besides, drug characteristics, dosing frequency, and side effects significantly influence adherence. Patients might find it difficult to follow complicated dosing schedules, encounter adverse effects, or believe that medications are either ineffective or too expensive, all of which can contribute to decreased adherence to the therapies.[19]

RELEVANCE

Atrial fibrillation is one of the most common sustained cardiac arrhythmias and is associated with a high risk of ischemic stroke, cardiovascular complications, and mortality [1–3,8]. Direct oral anticoagulants are widely used for the prevention of thromboembolic complications in patients with atrial fibrillation and are currently considered standard therapy [9,10]. However, the effectiveness of this therapy largely depends on long term patient adherence to medication, since missed doses reduce the level of anticoagulant protection [25,26]. Despite the accumulation of a large body of clinical evidence, results from different studies demonstrate variability in adherence and treatment persistence among individual NOAC agents [33–38]. In addition, factors determining reduced adherence, including dosing regimens, drug tolerability, and dosing errors, are described in the literature in a fragmented manner [39–42]. As a result, it remains insufficiently clear which clinical and organizational factors most strongly determine the long term effectiveness of anticoagulant therapy in patients with atrial fibrillation.

SCIENTIFIC NOVELTY

The scientific novelty of this study lies in the comprehensive synthesis and analytical systematization of current evidence on adherence and treatment persistence to direct oral anticoagulants in patients with atrial fibrillation, taking into account differences between individual NOAC agents. Within this narrative review, a comparative analysis of adherence and treatment persistence among the main NOAC agents is performed, and data on clinical outcomes associated with differences in treatment adherence are summarized. In addition, clinical and organizational factors influencing adherence are examined, including dosing regimens, drug tolerability, and dosing errors. Such analytical synthesis allows a more comprehensive understanding of the factors determining the effectiveness of long term anticoagulant therapy in atrial fibrillation.

AIM

The aim of this narrative review is to summarize current evidence on adherence and persistence to NOAC therapy in atrial fibrillation, to compare these indicators between individual agents, and to analyze factors influencing treatment adherence and associated clinical outcomes.

RESEARCH OBJECTIVES

To achieve this aim, the following research objectives were formulated.

1. To analyze current publications addressing adherence and persistence to direct oral anticoagulant therapy in patients with atrial fibrillation.
2. To compare adherence and treatment persistence among the main NOAC agents.
3. To summarize evidence on clinical outcomes associated with differences in treatment adherence.
4. To analyze factors associated with reduced adherence, including dosing regimens, drug tolerability, dosing errors, and socioeconomic conditions of treatment.
5. To systematize data on potential clinical and organizational strategies aimed at improving adherence to anticoagulant therapy.

METHODS

LITERATURE SEARCH AND STUDY SELECTION

This study was conducted as a narrative literature review using the PubMed and Google Scholar databases. A structured search strategy was applied to identify relevant publications published between 2015 and 2025 involving adult patients. The search included combinations of the following keywords: NOAC, DOAC, VKA, compliance, adherence, persistence, atrial fibrillation, stroke prevention, and bleeding risk. Search terms were combined using Boolean operators AND and OR. When available, Medical Subject Headings were also considered to improve the sensitivity of the search.

Titles and abstracts of the retrieved records were screened for relevance, followed by full text assessment of potentially eligible publications. Reference lists of the selected articles were additionally screened in order to identify further relevant studies that were not captured during the initial database search. Study selection and data extraction were performed by the authors involved in the literature search.

A total of 57 publications were reviewed. The analysis focused on studies addressing adherence, persistence, dosing practices, and clinical outcomes associated with NOAC therapy in patients with atrial fibrillation. Extracted information included study design, study population, adherence indicators, persistence rates, dosing patterns, and reported clinical outcomes. Particular attention was given to commonly used adherence indicators such as medication possession ratio and proportion of days covered. Due to heterogeneity in study designs and outcome definitions, a qualitative synthesis of the available evidence was performed rather than a quantitative meta analysis.

INCLUSION CRITERIA

Original clinical studies, meta analyses, systematic reviews, and European clinical guidelines concerning the use of NOAC for the prevention of stroke and systemic embolism in patients with atrial fibrillation were eligible for inclusion. Studies examining adherence and persistence in medical therapy were also considered relevant. Some of the included studies involved broader populations treated with NOAC and were not restricted exclusively to patients with atrial fibrillation. Only publications written in English and published between 2015 and 2025 were included.

EXCLUSION CRITERIA

Studies focused exclusively on pediatric populations were excluded. Case reports and conference abstracts were also excluded due to their limited methodological value and insufficient data for comparative analysis.

HANDLING OF EDOXABAN DATA

Edoxaban is a relatively newer anticoagulant and was not included in many of the reviewed studies. Edoxaban was not analyzed separately due to limited and heterogeneous data in the reviewed publications. In studies evaluating multiple NOAC including edoxaban, data related to rivaroxaban, dabigatran, or apixaban were included, whereas information specific to edoxaban was omitted to maintain methodological consistency of the comparison.

BODY OF REVIEW

STROKE AND MAJOR BLEEDING RISK

To date, many systematic reviews and meta-analyses have thoroughly examined the key NOAC used in patients with AF, evaluating their efficacy and safety.

In a network meta- analysis performed by López-López et al. (2018) 23 randomised trials involving 94 656 patients were analysed to compare the safety, efficacy, and cost effectiveness of individual NOAC in patients with AF. Compared with dabigatran 150 mg twice daily, rivaroxaban 20 mg once daily showed a higher risk of stroke or systemic embolism. Differences in ischaemic stroke risk among approved NOAC doses were minimal. Apixaban 5 mg administered twice a day showed the lowest risk of major and intracranial bleeding compared with other standard-dose NOAC. Dabigatran 150 mg twice daily and rivaroxaban 20 mg once daily were associated with higher rates of major and intracranial bleeding relative to apixaban and rivaroxaban also had higher intracranial bleeding risk than dabigatran. Most NOAC (except rivaroxaban 20 mg once daily) reduced intracranial bleeding risk by more than 50%. For clinically relevant non-major bleeding, rivaroxaban 20 mg once daily demonstrated higher risks compared with apixaban 5 mg twice daily. Overall, apixaban 5 mg twice daily was identified as the most effective treatment across multiple assessed outcomes, including stroke or systemic embolism, myocardial infarction, and all-cause mortality. It was also considered the safest option, demonstrating the lowest rates of major and gastrointestinal bleeding.[10]

Noseworthy et al. (2016) brought three one-to-one propensity-score-matched cohorts of patients with nonvalvular AF who were users of NOAC. For the primary effectiveness outcome of stroke or systemic embolism, no meaningful differences were observed among the NOAC. Dabigatran, rivaroxaban, and apixaban also showed comparable risks of both ischemic and hemorrhagic stroke. Compared with dabigatran, rivaroxaban was linked to a higher risk of major

bleeding and intracranial bleeding. Relative to dabigatran, apixaban showed a lower risk of major bleeding and a tendency toward a reduced risk of intracranial bleeding. When compared with rivaroxaban, apixaban was likewise associated with a lower risk of major bleeding and appeared to have a lower risk of intracranial bleeding. In subgroup analyses, rivaroxaban demonstrated a consistently higher risk of major bleeding than either dabigatran or apixaban across all CHA_2DS_2-VASc and HAS-BLED categories. These findings indicate that dabigatran, rivaroxaban, and apixaban offer comparable effectiveness in reducing stroke or systemic embolism. In addition, apixaban appears to be linked to a lower risk of major bleeding, whereas rivaroxaban is associated with a higher risk.[20]

Proietti et al. (2018) conducted a systematic review and meta-analysis of all observational real-world studies comparing apixaban with dabigatran and rivaroxaban. (170 814 patients treated with apixaban were included in the 16 studies). Apixaban and dabigatran showed generally comparable risks of thromboembolic events and stroke, although reduced-dose apixaban was associated with a lower thromboembolic risk. Major bleeding was significantly less frequent with apixaban, and apixaban also demonstrated lower risks of gastrointestinal bleeding and any bleeding, with no difference in intracranial hemorrhage. When compared with rivaroxaban, apixaban was associated with significantly higher risks of thromboembolic events and stroke while showing significantly lower risks of major bleeding, intracranial hemorrhage, and gastrointestinal bleeding.[21]

Lip et al. (2016) performed network meta-analysis, including data from four Phase III randomised controlled trials: ARISTOTLE, RE-LY, ROCKET-AF, and ENGAGE AF-TIMI 48 which affected > 70,000 patients with non-valvular AF. ARISTOTLE and RE-LY enrolled patients with a $CHADS_2$ score ≥1, whereas ROCKET-AF and ENGAGE AF-TIMI 48 included higher-risk patients with a $CHADS_2$ score ≥2. Across trials, few significant efficacy differences were observed among NOAC. High-dose dabigatran was more effective than rivaroxaban and low-dose dabigatran, but not apixaban. Regarding safety, apixaban showed significantly lower risks of major bleeding, gastrointestinal bleeding, and other major bleeding than rivaroxaban and dabigatran 150 mg. Dabigatran and apixaban demonstrated significantly lower intracranial hemorrhage risk than rivaroxaban, which also carried a higher risk of clinically relevant non-major bleeding compared with all other NOAC reported.[22]

COST-EFFECTIVENESS ANALYSIS

The cost-effectiveness analysis made by López-López et al. (2018) showed that expected lifetime total costs regarding individual NOAC in the UK were £23064 for dabigatran 150 mg twice daily which had quality adjusted life years (QALYs) - 5.42, and £24 841 for rivaroxaban 20 mg once daily (QALYs = 5.45). Apixaban 5 mg administered twice a day had the highest expected QALYs = 5.49, with expected total costs £23340 which may suggest it can be considered as the best NOAC.[10]

Wu et al. (2021) performed a 10-year Markov model to evaluate the long-term clinical and economic outcomes in atrial fibrillation patients over 75 years of age receiving either NOAC or warfarin in the US. The model incorporated a hypothetical cohort of 10,000 patients within this age group. Among individual NOAC, excluding edoxaban, apixaban was the preferred treatment strategy for AF patients aged over 75 years with expected total costs $30,671.69 and QALYs 5.53.[23]

Lorenzoni et al. (2021) study has shown that apixaban with overall costs €15245 and QALYs 5.90 is a cost-saving and safe alternative to other NOAC among patients with AF in the Italian healthcare setting.[24]

ADHERENCE AND PERSISTENCE

Adherence to the therapy is one of the most important factors contributing to clinical success. Improving a patient's adherence to the medication may be more impactful on the patient's health than discovering and implementing any new therapeutic options.[25] Reduced adherence to NOAC therapy is associated with elevated risk of thromboembolism, all-cause mortality and hemorrhagic events. To ensure effective stroke prevention in patients with AF taking NOAC, a minimum adherence rate of 90% is required.[26]

NOAC are less prone to discontinuation than VKA because of no need for monitoring, fewer drug interactions and easier dosing. Nevertheless, up to 50% of patients discontinue NOAC therapy.[27] We examined prescribing patterns of individual NOAC, reviewed and compared patient adherence and persistence with the anticoagulant treatment with NOAC in AF, and evaluated physician prescribing practices with particular emphasis on dosing regimens, in order to identify factors underlying observed differences among these agents.

PRESCRIBING PATTERNS

Across multiple studies, rivaroxaban has consistently been reported as the most frequently prescribed NOAC, followed by apixaban and dabigatran, however, prescribing patterns vary between countries, healthcare system, and study period. According to the recent study by Yang et al (2023) performed in the 65 countries worldwide from 2008 to 2019 rivaroxaban accounted for the highest proportion of NOAC consumption (35-100%) in 70% of these countries,

while dabigatran generated less than 33% of the total NOAC sales.[28] Table 1 presents selected large observational studies from North America, East Asia and Europe and summarizes regional prescribing patterns of the main NOAC together with the corresponding study populations and study periods.

Table 1. Prescribing patterns of individual NOAC in large observational studies from different regions

Study	The most frequently prescribed NOAC	Study population	Region	Study Period
Kjerpeseth et al (2017)[29]	Rivaroxaban (33.86%) apixaban (33.99%) dabigatran (32.15%)	37,000	Norway	2010-2015
Haastrup et al (2018)[30]	Rivaroxaban (41.38%) apixaban (21.40%) dabigatran (37.15%)	126,691	Denmark	2008-2016
Zhang et al (2022) [31]	Rivaroxaban (72.88%) apixaban (0.31%) dabigatran (26.80%)	59,489	China	2010-2020
Wheelock et al (2021)[32]	Rivaroxaban (15.34%) apixaban (15.15%) dabigatran (4.63%)*	2,062,609	United States	2013-2018

**percentages apply to the proportion of total NOAC prescriptions rather than to the number of individual patients receiving a given NOAC*
***Edoxaban is not presented in the table because studies focusing exclusively on edoxaban or containing limited and heterogeneous data were excluded from the analysis.*

PATIENT ADHERENCE AND PERSISTENCE

According to the study conducted by Coleman et al. (2016) adherence declined throughout the 24-month follow-up period for both rivaroxaban and dabigatran. Importantly, mean absolute PDC was higher for rivaroxaban in comparison to dabigatran at 3, 6, 12 and 24 months. Rivaroxaban users' PDC was also more likely to be ≥80% at every measured time period. Lower adherence to dabigatran potentially resulted in a 10% increased relative hazard of death or stroke.[33]

In the study by Komen et al. (2021) performed in five Western European countries over 5 years of follow-up adherence and persistence were relatively high. Persistence of NOAC treatment decreased to 82% after 1 year and to 63% after 5 years. After including patients who restarted NOAC treatment, after 5 years 85% of patients were adequately treated. Adherence and persistence to the therapy were lower with dabigatran compared to apixaban and rivaroxaban.[34]

Research by Pinto et al. (2018) conducted in Portugal reported the highest adherence with rivaroxaban, followed by dabigatran and apixaban respectively. Additionally, dabigatran had the lowest proportion of adequate dosage prescriptions, only 50.1%, compared to 81.6% guideline-consistent doses in rivaroxaban and 78.7% in apixaban. As a result, the fewest patients achieved therapeutic goals while being treated with dabigatran.[35]

Study by Brown et al. (2017) analyzed patients' adherence and persistence to NOAC therapy in the USA at 3, 6, and 9 months of follow-up. Adherence was lower for dabigatran in each time period and comparable between rivaroxaban and apixaban.[36]

An analysis by Grymonprez et al. (2022) presented the results suggesting relatively small differences between adherence and persistence among individual NOAC. The highest adherence was to rivaroxaban and the lowest to apixaban. Lower adherence was potentially associated with NOAC dosed twice a day. However persistence was the highest for apixaban and the lowest for rivaroxaban. Half of patients treated with apixaban had discontinued therapy after 3.76 years, compared to 3.49 and 3.12 for dabigatran and rivaroxaban respectively.[37]

Study by Wirbka et al. (2021) examined claims data of insured persons in Germany. Results indicated the highest adherence to apixaban and the lowest to dabigatran. Furthermore, the researchers found that a 10% reduction in adherence was associated with a 3%, 5%, and 2% increase in stroke risk for apixaban, rivaroxaban, and dabigatran,

respectively.[38] Table 2 summarizes selected observational studies evaluating adherence and persistence to NOAC therapy in patients with atrial fibrillation.

Table 2. Adherence and persistence to NOAC therapy in selected observational studies in patients with atrial fibrillation.

Study	Compared NOAC	Study population	Adherence	Persistence
Coleman et al. (2016)[33]	Rivaroxaban, Dabigatran	21,756	Rivaroxaban (49%) Dabigatran (38%)*	
Komen et al. (2021)[34]	Rivaroxaban, Dabigatran, Apixaban	559,445	Rivaroxaban (83%) Dabigatran (77%) Apixaban (86%)	Rivaroxaban (75%) Dabigatran (65%) Apixaban (75%)
Pinto et al. (2018)[35]	Rivaroxaban, Dabigatran, Apixaban	21,854	Rivaroxaban (56.3%) Dabigatran (55.3%) Apixaban (53.3%)	
Brown et al. (2017)[36]	Rivaroxaban, Dabigatran, Apixaban	15,341	Rivaroxaban (66%) Dabigatran (57%) Apixaban (66%)**	
Grymonprez et al. (2022)[37]	Rivaroxaban, Dabigatran, Apixaban	277,782	Rivaroxaban (91.3%) Dabigatran (88.6%) Apixaban (87.8%)***	Rivaroxaban (67.1%) Dabigatran (68.1%) Apixaban (69.8%)****
Wirbka et al. (2021)[38]	Rivaroxaban, Dabigatran, Apixaban	10,092	Rivaroxaban (80%) Dabigatran (70%) Apixaban (81%)	

**Only results at 9 month follow-up were presented in the table*
***Only results at 24 month follow-up were presented in the table*
****Only results at 12 month follow-up were presented in the table, adherence defined as PDC≥ 90%*
*****Only results at 12 month follow-up were presented in the table.*
******Persistence data were reported only in studies where these outcomes were available.*

DOSING

Major differences between NOAC that may substantially affect drug adherence and persistence are distinct dosage regimens. In accordance with European Society of Cardiology (ESC) guidelines standard dose is 20 mg administered once a day for rivaroxaban, 5 mg administered twice a day for apixaban and 150 mg administered twice a day for dabigatran.[39]

A crucial factor for effectiveness of anticoagulant treatment is appropriate dosing of NOAC. Kidney function, age, and body weight are key factors to consider when determining the appropriate NOAC dosage. This is reflected in the respective Summaries of Product Characteristics (SPCs) and drug labels, which differ for each NOAC and vary across regulatory agencies, which have issued distinct SPCs for the three NOAC examined in this paper. These discrepancies limit prescribing practices and contribute to confusion regarding dosing rules, despite efforts to harmonize guidance in European consensus documents. Even though the dosages mentioned above are well known and available in guidelines for each country, cases of incorrect dosing are common in clinical practice.[40]

Camm et al. (2020) study shows that in 10426 patients taking NOAC 23.2% were underdosed and 3.8% were overdosed. Both non-recommended dosing in general and underdosing were linked to an increased risk of all-cause mortality, while no significant elevation in the risk of stroke or systemic embolism was observed. As anticipated, underdosing was associated with a markedly reduced risk of bleeding.[41]

In Zhang et al. 's (2021) meta-analysis, 16 adjusted studies including 130 609 patients with AF worldwide were analyzed. Among about 38 000 patients with off-label dosing of NOAC the principal findings indicated that off-label underdosing of NOAC was associated with a significantly increased risk of ischemic stroke (IS), systemic embolism (SE), all-cause mortality, and adverse net clinical outcomes compared with on-label dosing, without a corresponding reduction in major bleeding risk. The limited available data on off-label overdosing suggested a potential association with elevated risks of IS/SE and major bleeding relative to on-label dosing. Furthermore, subgroup analyses of off-label underdosing for IS/SE revealed heterogeneity across different NOAC. Off- label underdosing of rivaroxaban and apixaban was associated with increased risk of major bleeding compared with on-label dosing whereas off-label underdosing of dabigatran was associated with decreased risk of major bleeding compared with on-label dosing.[42]

Moudallel et al (2018) showed that improper NOAC dosage regimens are common among the hospitalized patients. Suboptimal treatment has been observed in 29.7% of patients treated with apixaban, 23.4% with dabigatran, and 21.9% with rivaroxaban. Underdosing has been more prevalent than overdosing, especially in apixaban reaching 24.5% of patients and 4.5% of patients respectively.[43] In different studies incorrect dosage regimens have been noted in 32% of patients,[44] 14.4 % of patients,[45] 26.2% of patients[46] and 28% of patients[41] with underdosing being generally more prevalent in most of the research.

DISCUSSION

Reduced renal function is a key determinant of dabigatran dosing due to its predominantly renal elimination. Current guidelines recommend dose reduction in patients with moderate renal impairment and avoidance in severe renal dysfunction, with regular reassessment of renal function to prevent drug accumulation and bleeding.

Inadequate estimation of renal function is a documented cause of incorrect NOAC dosing, particularly in elderly patients with low creatinine clearance. Studies have shown that clinicians frequently overestimate renal function by relying on eGFR instead of Cockcroft–Gault equation, or by not reassessing renal function regularly, resulting in overdosing in patients with impaired kidney function, or underdosing when physicians are overly cautious.[47-48]

Overdosed patients, due to underestimated CrCl, experience more bleeding, dyspepsia or bruising, which drives early non-persistence. They interpret these events as harmful effects of therapy and often stop medication without consulting clinicians. When dealing with the elderly, some physicians have a tendency to underdose their medication, being overly cautious or unsure of currently proposed guidelines. (GARFIELD-AF,[49] ORBIT II-AF[48]) These patients are most affected, as they are both the most likely to have miscalculated renal function and the most sensitive to side effects, making their adherence particularly vulnerable. When major CVEs occur in underdosed patients, confidence in the therapy is reduced, leading to long term poor adherence. Frequent dose changes due to late recognition of renal decline, combined with repeated or poorly explained laboratory monitoring, can make therapy seem unstable or unsafe to patients, leading to confusion, reduced confidence, and ultimately poorer adherence.[48-49]

Dabigatran has repeatedly been shown to have lower adherence and persistence compared with factor Xa inhibitors, a finding attributed to pharmacological, tolerability, and practical factors. Its twice-daily dosing, may be associated with poorer adherence.[50] Dyspepsia possibly related to the tartaric acid core of the capsule represents another major cause of non-persistence. Observational cohorts and claims-based analyses have consistently shown high rates of early discontinuation with dabigatran due to GI intolerance.[51-52]

Comparative analyses of adherence in atrial fibrillation suggest that rivaroxaban and apixaban achieve broadly similar adherence rates across studies. Although rivaroxaban benefits from a once - daily dosing regimen, this advantage appears to diminish over time, as several papers report lower persistence compared with apixaban. Apixaban, despite its twice-daily schedule, demonstrates more sustained treatment continuation, potentially reflecting better tolerability and safety. Overall, while adherence between the two agents remains closely comparable, differences in persistence diminish the expected benefit of simpler dosing with rivaroxaban.[37-38]

The systematic review by Vervloet evaluated evidence on the effectiveness of electronic reminders, such as SMS alerts, pager messages, and audiovisual device prompts to improve adherence to long-term medication regimens. They identified 13 relevant studies examining patients on chronic therapy and found that electronic reminders were generally effective at improving short-term adherence, with most SMS reminder interventions showing significant positive effects and several device-based reminders also demonstrating benefits. However, the majority of evidence came from short follow-up periods typically less than six months, and long-term effects on sustained adherence remain unclear, highlighting the need for further research into the durability of digital reminder strategies and their impact on clinical outcomes. If implemented, such solutions could form a backbone of an integrated care model, where the input of both physician and patient in day to day medication management, as well as in other fields, could be minimal. One can wonder what kind of new horizons the rapid development of AI could usher into medicine.[53]

Suboptimal adherence in NOAC therapy in atrial fibrillation remains a multifactorial problem, influenced both by prescribing practices and patient - related factors. Improper dosing by physicians may be reduced through stricter implementation of guideline based algorithms, regular reassessment of relevant organ functions, and wider use of clinical decision support systems based in electronic health records. NOAC are also widely used in the treatment and secondary prevention of deep vein thrombosis, where sustained adherence is critical to prevent recurrence and post-thrombotic complications. Similar to atrial fibrillation, simplified dosing regimens and reduced monitoring requirements with NOAC may improve adherence.

Improvements in clinical practice should also include greater continuity of care, such as the use of individualized patient care plans, like IKP models implemented in Poland (an integrated system of medical documentation, prescriptions, and patient care currently in use and in development), and a more active role for pharmacists and nurses in monitoring medication use, reinforcing education, and identifying non-adherence.

Although routine laboratory monitoring is not required for NOAC, selective assessment of clotting parameters or drug levels in high-risk patients may improve safety and confidence, analogous to monitoring strategies used with VKAs. Patient compliance could be further enhanced through digitalisation, clear and repeated communication regarding treatment goals, structured adherence assessment tools such as the Morisky Adherence Test, simplified dosing regimens, larger package sizes to reduce refill frequency and cost, and improved disease awareness.

Global inequalities substantially contribute to differences in adherence, with limited access to healthcare, medication cost barriers, underprescription of NOAC in lower-income settings, and insufficient government reimbursement programs all negatively impacting long-term compliance.

High rates have been reported in Western Europe and Japan, supported by universal healthcare coverage, structured follow-up, and integrated care models, as demonstrated in large registries such as GARFIELD-AF[49] and ORBIT-AF. [48] Countries including Germany, the Netherlands, and the Nordic states benefit from active pharmacist involvement and electronic prescribing systems, which have been associated with improved persistence.[54] Japan shows particularly high adherence, although dose reductions are frequent, as observed in the J-ROCKET AF and real-world Japanese cohort studies.[55]

In contrast, the United States demonstrates marked heterogeneity, with lower adherence linked to high out-of-pocket costs, fragmented care, and insurance related therapy switching, as shown in claims based analyses.[56] Middle income countries, including parts of Eastern Europe and Latin America, report moderate adherence largely dependent on reimbursement; partial coverage programs in Poland have been associated with increased NOAC uptake and persistence.[57] In low-income regions, anticoagulation remains underused due to limited access, affordability, and follow up, leading to early discontinuation.

SYNTHESIS OF RESULTS

The reviewed studies demonstrate that adherence and treatment continuation during NOAC therapy in patients with atrial fibrillation remain heterogeneous across different drugs and patient populations [33–38]. In most observational cohorts, rivaroxaban and apixaban show higher adherence compared with dabigatran, whereas persistence with therapy appears to be more sustained with apixaban in long term follow up [33–38]. Differences in dosing regimens, drug tolerability, and the frequency of adverse effects contribute to these variations [39–42]. In addition, incorrect dosing practices, particularly underdosing related to renal function concerns or clinical uncertainty, are frequently observed and may negatively influence both adherence and clinical outcomes [41–42].

The literature also indicates that adherence is influenced by multiple clinical and organizational factors, including patient age, polypharmacy, complexity of dosing schedules, and socioeconomic conditions [17–19]. Reduced adherence and premature discontinuation of anticoagulant therapy are consistently associated with increased risk of thromboembolic events, hospitalization, and mortality [25–26]. Taken together, the available evidence suggests that both pharmacological characteristics of individual NOAC and healthcare system related factors play a role in

determining long term treatment effectiveness .

STUDY LIMITATIONS

Several limitations should be considered when interpreting the findings of this review. First, the study was conducted as a narrative review rather than a systematic review or meta analysis, which limits the possibility of quantitative comparison between studies. Second, the included publications demonstrate substantial heterogeneity in study design, patient populations, follow up periods, and definitions of adherence and persistence, which complicates direct comparison of results. Third, the literature search was limited to two databases and to publications written in English between 2015 and 2025, which may have led to the exclusion of relevant studies published in other languages or indexed in additional databases.

Despite these limitations, the reviewed literature provides consistent evidence that adherence to anticoagulant therapy remains a critical determinant of clinical outcomes in patients with atrial fibrillation [25–26,33–38]. Understanding the factors that influence adherence and treatment persistence is therefore essential for optimizing long term anticoagulant therapy and improving stroke prevention strategies in clinical practice. These findings form the basis for the following conclusions.

CONCLUSIONS

1. Analysis of published observational studies shows that adherence and treatment persistence to direct oral anticoagulants in patients with atrial fibrillation differ substantially between individual agents. The lowest adherence rates are most often observed with dabigatran, whereas factor Xa inhibitors, particularly rivaroxaban and apixaban, demonstrate higher levels of treatment adherence in most studies.
2. In several observational cohorts higher adherence has been reported with rivaroxaban and apixaban, whereas longer treatment persistence in some studies has been observed with apixaban.
3. Incorrect dosing of direct oral anticoagulants represents a common problem in real world clinical practice. Deviations from guideline recommended dosing regimens are identified in a substantial proportion of patients, with underdosing occurring more frequently than overdosing and potentially reducing the effectiveness of thromboembolic event prevention.
4. Adherence to anticoagulant therapy is determined by a combination of pharmacological characteristics of the drugs and patient related factors. Important determinants include dosing frequency, drug tolerability, adverse effects, advanced age, polypharmacy, and socioeconomic conditions of treatment.
5. Optimization of long term anticoagulant therapy requires individualized selection of the anticoagulant agent, appropriate dose adjustment according to renal function and clinical guidelines, and regular reassessment of risk factors that may influence treatment continuation.
6. Improvement of adherence and treatment persistence should be considered an important component of stroke prevention strategies in patients with atrial fibrillation and a key objective of clinical practice.

DISCLOSURE

AUTHORS' CONTRIBUTIONS

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Data presentation in the form of tables: Tomasz Klinkosz.

All authors approved the final version of the manuscript.

STATEMENT ON THE USE OF ARTIFICIAL INTELLIGENCE

Artificial intelligence tools were used exclusively for the identification and correction of linguistic, grammatical, and

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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