Patient Preference and Adherence

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STUDY PROTOCOL

Pharmacist-Led Intervention to Enhance Direct Oral Anticoagulant Adherence and Treatment Outcomes in Atrial Fibrillation: A Pragmatic Clinical Trial

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Purpose: This study aims to evaluate the impact of a pharmacist-led education program on medication adherence and treatment outcomes among patient with atrial fibrillation (AF) using direct oral anticoagulants (DOACs) for stroke prevention. Additionally, we will compare self-reported adherence with claims data and examine whether DOAC blood concentration can serve as a biomarker for medication adherence and treatment outcomes.

Patients and Methods: We will conduct a pragmatic randomized controlled trial at National Taiwan University Hospital (NTUH). Patients aged 18 years or older, diagnosed with AF, and newly initiated on DOACs for primary or secondary stroke prevention will be randomized to either the intervention or control group. The intervention group will receive pharmacist-led education at baseline; the control group will receive usual care. The primary endpoint is patients' self-reported medication-use behavior, measured by the Traditional Chinese version of the Adherence to Refills and Medications Scale. We will also compare self-reported adherence with an objective adherence indicator, the DOAC trough concentration, determined by ultra-high-performance liquid chromatography coupled with tandem mass spectrometry. After randomization, participants will return to their routine clinical care, and all follow-up assessments will coincide with their regular clinic visits. Patients' DOAC use behaviors and blood concentrations will be measured at 3- and 6-month follow-ups. Baseline characteristics and treatment outcomes will be obtained from NTUH electronic medical records and the National Health Insurance claims data.

Conclusion: This trial will evaluate the effectiveness of pharmacist-led education in improving DOAC adherence and treatment outcomes over a 6-month follow-up period. The findings will inform the development and implementation of future pharmacist-led care models.

Trial Registration: The study protocol has been registered at ClinicalTrials.gov (identifier NCT07159399).

Keywords: pharmacist-led service, anticoagulation, pragmatic trial

Introduction

Atrial fibrillation (AF) is the most common arrhythmia, which increases the risk of ischemic stroke four- to five-fold.[1,2] Direct oral anticoagulants (DOACs) are preferred over warfarin for stroke prevention in patients with AF due to their predictable pharmacokinetics, fewer drug-food interactions, and the absence of routine monitoring requirements.[3–8] Despite these advantages, real-world adherence to DOACs remains inadequate,[9,10] and suboptimal adherence is associated with higher risks of both thromboembolic and bleeding complications.[11,12] Although oral anticoagulants (OACs) therapy effectively reduce stroke risk, their clinical benefits are often compromised by medication non-adherence, which ranges from 15% to 40%.[13] The World Health Organization has highlighted that improving adherence to long-term

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therapies could yield greater population health gains than advancements in medical treatment alone.[14] Nevertheless, current adherence interventions in AF have achieved only modest and inconsistent effects.[15,16]

Pharmacist-led anticoagulation services represent a promising strategy to improve adherence. Evidence from anticoagulation clinics (ACCs) indicates that pharmacist-managed warfarin therapy can improve safety and reduce thromboembolism and bleeding risks.[13] Yet evidence regarding the effectiveness of pharmacist-led interventions for DOAC users remains limited. Observational studies from the United States and China suggest that pharmacist-led ACCs, tailored monitoring, and telephone follow-up may support better adherence and improved clinical outcomes among DOAC users,[17,18] though non-randomized designs introduce potential residual confounding. In contrast, two recent randomized trials conducted in Japan and the United States did not show clear improvements in DOAC adherence with pharmacist-led interventions, likely due to already high baseline adherence, short follow-up periods, and insufficient power to detect differences in clinical outcomes.[19,20]

Given that these trials were conducted in healthcare systems unlike Taiwan, where the National Health Insurance (NHI) system minimizes refill barriers and result in high refill adherence despite inconsistent day-to-day medication-taking behavior, there is still a need to evaluate pharmacist-led interventions in a pragmatic, workflow-integrated manner within Taiwan's real-world clinical environment. This study evaluates the impact of a pharmacist-led education program on DOAC adherence and treatment outcomes in patients with AF who are newly initiating DOAC therapy in Taiwan. We hypothesize that the intervention will improve medication adherence and may support favorable treatment outcomes.

Materials and Methods

Study Aims

This study aims to investigate: (a) the impact of a pharmacist-led patient education program on DOAC adherence and treatment outcomes, (b) patients' medication-use patterns through a comparison of self-reported data with administrative claims, and (c) the potential role of DOAC blood concentrations as a biomarker for both medication adherence and treatment effectiveness among patients with AF who are newly prescribed DOACs for stroke prevention.

Study Design and Data Source

This study is a two-arm, pragmatic randomized controlled trial conducted at National Taiwan University Hospital (NTUH), a tertiary medical center in northern Taiwan. An overview of the study design and procedures is presented in Figure 1. Patients newly prescribed DOACs for stroke prevention will be recruited from NTUH outpatient clinics in collaboration with two attending physicians. Pharmacists will assist with preliminary screening to identify potential study candidates. Those patients will then be referred to the research team for confirmation of eligibility.

The intervention is grounded in the Social Cognitive Theory, with self-efficacy as the core mechanism driving behavior change. It is designed to enhance patients' understanding of anticoagulant therapy and build confidence in managing their medications. Pharmacists will provide individualized education and counselling to improve psychological capability and motivation, support patients in integrating DOAC use into their daily routines to facilitate behavioral regulation, and offer ongoing feedback and reinforcement to help maintain adherence. Within this framework, improved self-efficacy is posited as the key mediator linking the pharmacist intervention to sustained and effective medication-taking behavior.

Two primary data sources will be used: the electronic medical records (EMRs) from the NTUH and National Health Insurance (NHI) claims data from the Health and Welfare Database. The NTUH EMRs will be used for baseline assessment and eligibility verification, whereas NHI claims data will enable follow-up of clinical events and evaluation of patients' medication-use patterns.

Study Participants

Inclusion and Exclusion Criteria

Eligible participants are adults aged 18 years or older with a confirmed diagnosis of AF who are expected to begin DOAC therapy for at least 3 months for either primary or secondary stroke prevention. Patients will be excluded if they

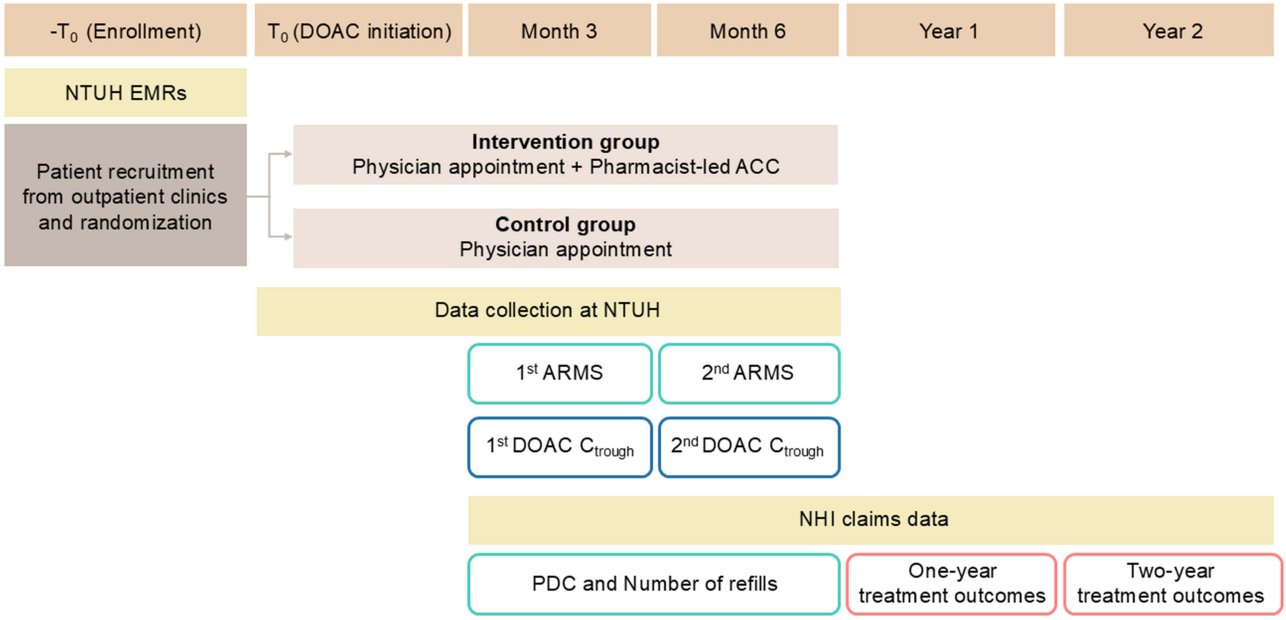

Figure 1 An overview of the study design and procedures.
Abbreviations: ACC, anticoagulation clinic; AF, atrial fibrillation; ARMS, adherence to refills and medications scale; C_{trough}, trough concentration; DOAC, direct oral anticoagulant; EMR, electronic medical record; NHI, National Health Insurance; NTUH, National Taiwan University Hospital; PDC, proportion of days covered.

are unable to understand DOAC related education because of low literacy, language limitations, or cognitive impairment. Additional exclusion criteria include prior DOAC therapy for more than six months, the presence of contraindications to DOAC therapy, the use of DOACs in off label dosing regimens, and pregnancy or breastfeeding.

Sample Size

Sample size estimation was performed using G*Power software.[21,22] A minimum of 128 participants is required to detect a moderate effect on medication adherence, assuming an effect size of Cohen's d = 0.5, a statistical power of 0.80, and a two-sided significance level of 0.05. To account for potential attrition, the study plans to recruit 200 participants (100 in per study arm). As the effect of the pharmacist-led intervention will be evaluated separately for patients receiving DOAC therapy for primary versus secondary prevention, we plan to enroll 200 participants in each category, yielding a total sample size of 400 participants.

Randomization

Eligible patients will first be stratified according to whether they are receiving DOAC therapy for primary or secondary prevention. Within each stratum, participants will be randomized in a 1:1 ratio to either the intervention or control group using a computer-generated randomization sequence prepared by an independent research member not involved in outcome assessment. Study personnel responsible for enrollment will assign participants according to this sequence and will therefore be aware of treatment allocation, consistent with the pragmatic design of the study. Those assigned to the intervention group will be referred to the pharmacist-led ACC for education, while those in the control group will receive usual care without pharmacist-delivered education. Both participants and pharmacists administering the intervention will be aware of group assignment. The principal investigator; however, will remain blinded until all follow-up assessments have been completed and will continue to be blinded throughout data analysis.

Intervention

Patients in the intervention group will receive an initial DOAC education session delivered by two pharmacists at the NTUH ACC. Established in 2012, the NTUH ACC is staffed by two clinical pharmacists and provides comprehensive education and follow-up services for patients using OACs, including both warfarin and DOACs. Since its inception, the

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ACC has served over 1000 patients, with more than 80% of warfarin users achieving therapeutic targets following pharmacist-led care.[23]

During the first ACC visit, pharmacists will provide structured education, covering: (1) the indication and rationale for DOAC therapy, (2) the name and appearance of the prescribed DOAC, (3) dosage, frequency, and timing of administration, (4) mechanism of action, (5) management of missed doses, (6) potential adverse effects and self-monitoring strategies, and (7) perioperative management. To support better understanding and self-management, patients will receive a DOAC educational leaflet, a pillbox, and a medication diary to promote adherence. They will also be encouraged to join the official ACC communication app account for timely consultation regarding missed doses, adverse effects, and upcoming medical procedures.

Two follow-up visits will be scheduled at 3 and 6 months after the baseline session. At the initial visit, the pharmacist will review each patient's EMR to ensure the prescribed DOAC regimen aligns with approved indications and will contact the prescriber if discrepancies are identified. During follow-up visits, the pharmacist will assess changes in laboratory values and concomitant medications, communicating any drug-related problems to the prescribing physician for resolution. The core components of the pharmacist-led ACC services are summarized in Figure 2. To ensure intervention fidelity, all pharmacists follow a standardized education checklist that outlines the essential elements of the intervention. Pharmacists delivering the intervention are trained based on this protocol, and documentation from each education session will be reviewed on a regular basis by the study team for quality assurance.

Outcome Measurement

Medication Use Behavior

The primary endpoint of this study is patients' self-reported medication-use behavior, including medication-taking and refill adherence. Self-reported adherence will be assessed using the 12-item Traditional Chinese version of the Adherence to Refills and Medications Scale (ChARMS-T), which includes eight items measuring medication-taking behavior and four items measuring refill adherence.[24,25] Higher scores indicate more barriers to medication-taking or refill. The ChARMS-T has demonstrated good internal consistency and strong correlations with both medication-taking and refill behaviors.[25] In this study, the total ChARMS-T score will serve as the primary continuous outcome.

In addition, medication behavior will be evaluated using pharmacy dispensing records from the NHI claims database. Medication-taking adherence will be quantified as the proportion of days covered (PDC) over the 3- and 6-month follow-up periods, whereas refill adherence will be assessed by the number of prescription refills during the same intervals. The

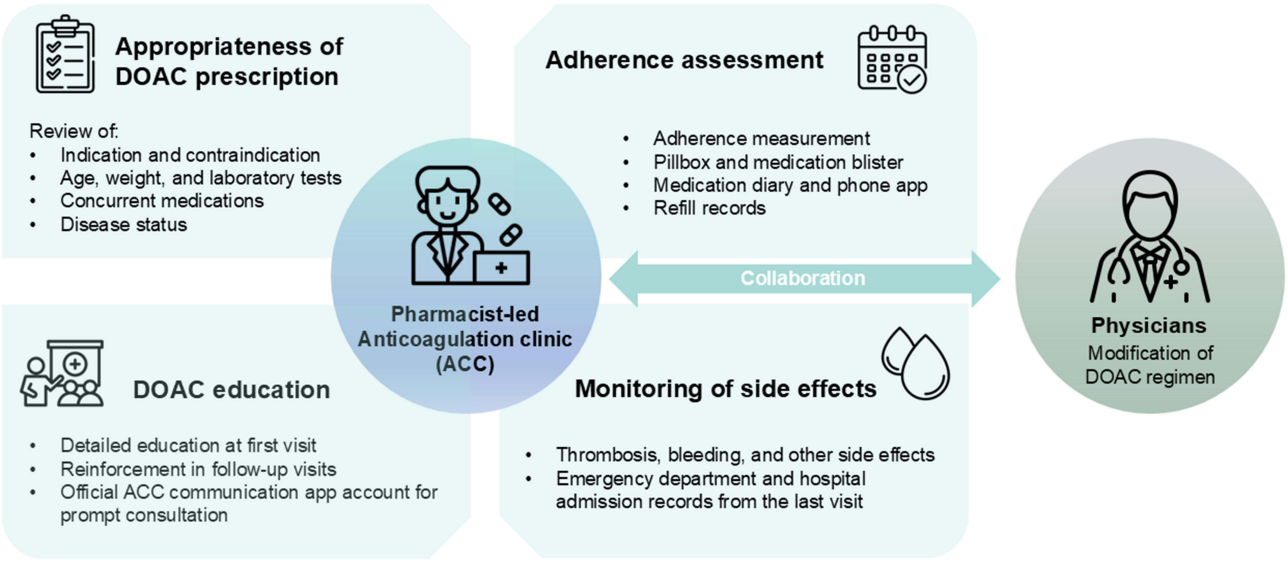

Figure 2 Key components of the pharmacist-led anticoagulant clinic services.
Abbreviation: DOAC, direct oral anticoagulant.

PDC will be calculated as the total number of days of DOAC supply during the 3- and 6-month follow-up periods, regardless of switching between DOACs, divided by the number of days in the respective follow-up period.

Treatment Outcomes

The secondary endpoint comprises treatment outcomes, including both effectiveness and safety outcomes, measured at one and two years following randomization. Effectiveness will be evaluated based on the occurrence of systemic thromboembolism events, including ischemic stroke, transient ischemic attack, myocardial infarction, coronary artery disease, peripheral artery disease, and venous thromboembolism. Safety outcomes will include major bleeding events, defined as intracranial hemorrhage, gastrointestinal bleeding, and other major bleeding episodes. All events will be identified through validated algorisms applied to inpatient admissions with primary discharge diagnosis codes recorded in the NHI claims database.[26–28]

Measurement of DOAC Blood Concentrations

To complement self-reported adherence, DOAC trough concentration will be measured as an objective adherence indicator. Blood samples will be obtained at the trough level, defined as the time immediately before the next scheduled DOAC dose. The allowable time window for sample collection is 22 to 26 hours after the previous dose of dabigatran or apixaban, and 10 to 14 hours after the previous dose of rivaroxaban or edoxaban. The time of the last DOAC dose and the time of blood sampling will be recorded and included as covariates when analyzing their association with drug concentrations. Measurement of DOAC concentrations will be performed using ultra high performance liquid chromatography coupled with tandem mass spectrometry (UHPLC MS/MS), an established and validated analytical method.[21]

Study Procedure

After enrollment and randomization, patients in the intervention group will receive a one-time baseline education session by a pharmacist, followed by two additional follow-up visits for medication review and monitoring of laboratory results. Participants in the control group will receive usual care composed of standard inpatient discharge counseling only and no outpatient education.

At the 3- and 6-month clinical visits, all participants will complete the ChARMS-T questionnaire, and DOAC trough concentrations will be measured. Medication adherence, including the PDC and the number of refills at 3 and 6 months, will be obtained from their NHI claims data. Treatment outcomes will be assessed for at one- and two-year follow-up using the NHI claims database.

Upon completion of data collection, analyses will include: (1) comparison of self-reported DOAC-use behavior (ChARMS-T scores) between groups, (2) comparison of clinical event rates between groups, (3) comparison of adherence based on self-reported versus NHI claims data, (4) correlations between self-reported adherence and DOAC concentrations, and (5) correlations between clinical outcomes and DOAC concentrations.

Ethical Consideration

This study protocol has been approved by the Institutional Review Board of National Taiwan University Hospital (NTUH-REC No.: 202404014RINC). All participants will provide written informed consent prior to study enrollment. Participant confidentiality and data security will be strictly maintained in accordance with the Declaration of Helsinki.

Statistical and Analytical Plan

Baseline characteristics of the participants will be summarized using descriptive statistics and compared between groups. Continuous variables will be analyzed with *t*-tests, and categorical variables will be compared using chi-square tests. Analyses will follow the intention-to-treat principle, with all randomized participants analyzed according to their assigned treatment arm. Post-randomization treatment changes will not affect group allocation, consistent with the pragmatic design. Missing data are expected to be minimal because demographic data and laboratory tests are recorded routinely in the hospital records. The most recent laboratory results within 6 months of DOAC initiation will be treated as

baseline values. If the level of missingness permits, complete-case analysis will be performed; otherwise, multiple imputation under a missing-at-random assumption will be used.

To evaluate the intervention impact on DOAC-use behavior, t-tests and linear regression models will be applied to assess between-group differences and estimate changes in ChARMS-T scores. Time-to-event analyses will be conducted to compare treatment outcomes between groups, with all-cause mortality as a competing risk. Stratified analyses by primary versus secondary prevention will examine potential heterogeneity of intervention effects. If heterogeneity is detected, an interaction term (intervention × prevention status) will be included in regression models, evaluated with the Wald test for adherence outcomes and likelihood ratio tests for treatment outcomes. Reasons for non-adherence will be explored by summarizing the frequency and percentage of responses to the ChARMS-T medication-taking items. The summary score for the medication-taking items will be correlated with the PDC using Pearson correlation, and refill adherence items will be correlated with NHI refill records.

The proportion of patients with DOAC concentrations within the expected therapeutic ranges will be compared between groups using chi-square tests. Because universally accepted therapeutic ranges are not established, expected trough ranges from clinical trials will be used. These ranges have been shown to be associated with clinical outcomes in our previous investigations.[29,30] Interpretation will account for pharmacokinetic variability, including renal function, age, body weight, and drug-drug interactions, and the pragmatic nature of sampling time. Although the UHPLC-MS/MS assay is precise and specific, minor analytical variation may occur. Thus, DOAC concentrations will be used primarily as an objective adherence indicator rather than for dose adjustment.

To examine the correlation between DOAC concentration and adherence, patients will be classified into high- and low-adherence groups based on the median ChARMS-T score, and proportions within therapeutic range will be compared using chi-square tests. To assess the correlation between DOAC concentrations and treatment outcomes, patients will be categorized into 3 groups according to DOAC concentration: above, within, or below the therapeutic range. The proportion of patients experiencing a clinical event will be compared across groups using chi-square tests. Analysis involving DOAC concentrations and clinical outcomes will be considered exploratory. All analyses will be performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), with a two-sided α level of 0.05.

Discussion

This randomized controlled trial is designed to evaluate the impact of pharmacist-led ACCs on medication adherence and treatment outcomes among patients receiving DOACs. While observational studies have suggested that pharmacist-led services may facilitate safer and more consistent DOAC use, recent randomized trials conducted in other health systems have not shown clear improvements in adherence.[17–20] Taiwan's healthcare environment, characterized by high medication accessibility yet suboptimal post-dispensing adherence, highlights the need to determine whether a pharmacist-led program embedded into routine practice can meaningfully improves patients' medication-taking behavior.

The intervention is developed from a patient-preference perspective, with shared decision-making and self-efficacy enhancement as core components to support sustained adherence. During the baseline counseling session, pharmacists review patients' daily routines, dosing preferences, and concerns about anticoagulant therapy. The counseling will be tailored to each patient's needs to help the patient integrate DOAC use into everyday life and build confidence in managing treatment. Through individualized education and scheduled follow-up visits, pharmacists encourage patients to voice questions and share their medication-use experiences, creating opportunities to address misconceptions and reinforce confidence in self-management. This approach fosters mutual understanding and strengthened self-efficacy, both of which are essential for long-term adherence.

Beyond evaluating adherence and treatment outcomes, this study aims to inform the development of more patient-centered models of anticoagulation care. By incorporating individualized counseling, shared decision-making, and structured follow-up, the pharmacist-led model reflects key principles of patient-centered practice and has the potential to improve patient engagement in the long-term management of DOAC therapy. If effective, this approach may promote closer pharmacist-physician collaboration and offer a feasible pathway for integrating pharmacist support into routine clinical workflows. The implications may extend beyond Taiwan to other health systems seeking to enhance patient-centered chronic disease management.

The study also provides a more comprehensive understanding of patients' medication use behavior. Reasons for non-adherence will first be explored using responses to individual ChARMS-T items, followed by a comparison of self-reported medication-taking and refill behaviors with pharmacy dispensing records from the NHI claims database. Given the easy

accessibility of medications and low copayments in Taiwan, we anticipate a discrepancy between refill and actual medication-taking. While high refill rates are expected in both groups, patients in the usual-care group may demonstrate poorer adherence to taking their medications as prescribed.

Although DOACs do not require routine laboratory monitoring due to predictable pharmacokinetic and pharmacodynamic profiles, the absence of concentration data contributes to uncertainty in therapeutic monitoring. Certain groups, such as patients with poor adherence or those with complex clinical conditions, may benefit from DOAC concentration testing.[31] This study aims to clarify the relationship between DOAC concentrations, adherence, and treatment outcomes. We anticipate a higher proportion of patients in the control group to have low DOAC concentrations compared with the intervention group, and that better adherence will correspond to concentrations within the expected therapeutic range. However, we hypothesize that the correlation between DOAC concentrations and treatment outcomes will be modest because thromboembolic and major bleeding events are relatively infrequent (approximately 1.8% and 3.0%, respectively).[32,33] In addition, DOAC concentrations may not fully reflect adherence due to their rapid onset of action. To address these challenges, the study incorporates repeated measures of DOAC concentrations. Despite the limitations, prior studies have consistently shown associations between DOAC levels and treatment outcomes,[29,34,35] and this trial will contribute additional evidence to guide therapeutic monitoring and clinical management.

Taken together, the study thoroughly evaluates the effectiveness of a pharmacist-led education program, provides new insights into medication-use behavior, and advances knowledge in both the pharmacokinetic and clinical management of DOACs. These considerations frame the context for interpreting the strengths and limitations of the present trial.

Strengths

This study presents the first pragmatic trial in Taiwan to evaluate the impact of a pharmacist-delivered pharmaceutical care program. Its pragmatic design strengthens the relevance and applicability of the findings and provides robust evidence of the value of pharmacist-led services. The intervention, consisting of a single education and two follow-up visits spaced 3 months apart, is simple, feasible, and closely aligned with routine clinical practice. Because DOAC dosing frequency resembles that of many commonly used chronic medications, such as antihypertensives, antidiabetic agents, and lipid-lowering drugs, the findings may be applicable to broader chronic disease management. The pragmatic nature of the study further supports the direct translation of the results into real-world clinical care and health policy.

A further strength is the study's focus on identifying reasons for DOAC non-adherence. In Taiwan, most patients refill their prescriptions, yet some may not take medications as prescribed, and this "post-dispensing non-adherence" is not captured by EMRs or claims data. By identifying underlying causes, such as forgetfulness or the perception that conditions are controlled, the findings will support the development of targeted education strategies and more effective patient–provider communication. This complements insights from secondary data sources and provides a more complete picture of adherence behaviors. Finally, a key innovation of our study is its examination of the relationship between DOAC concentrations and medication-use behavior. This offers an important contribution to existing evidence and addresses a key knowledge gap in understanding how drug levels relate to clinical outcomes.

Limitations

The primary endpoint relies on self-reported medication-use behavior, which may be subject to recall bias and social desirability bias. Participants may unintentionally misremember their medication-taking patterns or overestimate adherence to meet perceived expectations of physicians or study personnel. To mitigate these limitations, self-reported adherence from the ChARMS-T will be compared with DOAC blood concentrations as an objective adherence indicator. This triangulation approach is expected to enhance the credibility of our results.

Another limitation is that both patients and pharmacists are aware of intervention allocation. This may introduce performance bias, with participants in the intervention group making greater efforts to adhere to therapy or cooperate with the study. It may also lead to detection bias, as participants receiving the intervention might be more inclined to report favorable adherence behaviors on self-reported measures. In addition, the generalizability of our findings may be limited to tertiary medical centers operating within the Taiwan NHI system. Lastly, unlike warfarin, DOACs do not require routine therapeutic drug monitoring, and no universally accepted therapeutic range is available. Variations among DOAC agents, interpatient pharmacokinetic differences, and doses

adjustments further complicate the establishment of a consistent therapeutic threshold. These factors may increase the likelihood of misclassification when interpreting blood concentration results.

Conclusion

This proposed trial will evaluate the impact of pharmacist-led education on DOAC adherence and treatment outcomes. By providing deeper insights into medication-use behavior and examining the exploratory role of DOAC blood concentrations as an indicator of medication adherence and treatment outcomes, the study will inform the future development of pharmacist-led care models. If the intervention proves beneficial, the streamlined workflow may be scalable within routine pharmacy practice and compatible with implementation under the NHI system. The design also aligns with patient-preference principles by incorporating individualized counseling and shared decision-making to support acceptability and patient engagement.

Abbreviations

ACC, anticoagulation clinic; AF, atrial fibrillation; ARMS, adherence to refills and medications scale; DOAC, direct oral anticoagulant; EMR, electronic medical record; NHI, National Health Insurance; NTUH, National Taiwan University Hospital; PDC, proportion of days covered.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Benjamin EJ, Muntner P, Alonso A. et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. *Circulation*. 2019;139(10):e56–e528. doi:10.1161/CIR.0000000000000659
2. Chien KL, Su TC, Hsu HC, et al. Atrial fibrillation prevalence, incidence and risk of stroke and all-cause death among Chinese. *Int J Cardiol*. 2010;139(2):173–180. doi:10.1016/j.ijcard.2008.10.045
3. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2021;42(5):373–498. doi:10.1093/eurheartj/ehaa612
4. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2019;74(1):104–132. doi:10.1016/j.jacc.2019.01.011
5. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139–1151. doi:10.1056/NEJMoa0905561
6. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2013;369(22):2093–2104. doi:10.1056/NEJMoa1310907
7. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365(11):981–992. doi:10.1056/NEJMoa1107039
8. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365(10):883–891. doi:10.1056/NEJMoa1009638
9. Ozaki AF, Choi AS, Le QT, et al. Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation: a systematic review and meta-analysis. *Circ Cardiovasc Qual Outcomes*. 2020;13(3):e005969. doi:10.1161/circoutcomes.119.005969
10. Chen PT, Wang TJ, Hsieh MH, et al. Anticoagulation adherence and its associated factors in patients with atrial fibrillation: a cross-sectional study. *BMJ Open*. 2019;9(9):e029974. doi:10.1136/bmjopen-2019-029974
11. Kim D, Yang PS, Jang E, et al. The optimal drug adherence to maximize the efficacy and safety of non-vitamin K antagonist oral anticoagulant in real-world atrial fibrillation patients. *Europace*. 2020;22(4):547–557. doi:10.1093/europace/euz273
12. Shehab A, Bhagavathula AS, Abebe TB, et al. Patient Adherence to Novel Oral Anticoagulants (NOACs) for the treatment of atrial fibrillation and occurrence of associated bleeding events: a systematic review and meta-analysis. *Curr Vasc Pharmacol*. 2019;17(4):341–349. doi:10.2174/1570161116666180123111949
13. Hou K, Yang H, Ye Z, Wang Y, Liu L, Cui X. Effectiveness of pharmacist-led anticoagulation management on clinical outcomes: a systematic review and meta-analysis. *J Pharm Pharm Sci*. 2017;20(1):378–396. doi:10.18433/j3sq0b
14. World Health Organization. *Adherence to Long-Term Therapies: Evidence for Action*. Geneva: World Health Organization; 2003.
15. Gebreyohannes EA, Mill D, Salter S, Chalmers L, Bereznicki L, Lee K. Strategies for improving guideline adherence of anticoagulants for patients with atrial fibrillation in primary healthcare: a systematic review. *Thromb Res*. 2021;205:128–136. doi:10.1016/j.thromres.2021.07.014

16. Chung MK, Eckhardt LL, Chen LY, et al. Lifestyle and risk factor modification for reduction of atrial fibrillation: a scientific statement from the American Heart Association. *Circulation*. 2020;141(16):e750–e772. doi:10.1161/CIR.0000000000000748
17. Shore S, Ho PM, Lambert-Kerzner A, et al. Site-level variation in and practices associated with dabigatran adherence. *JAMA*. 2015;313 (14):1443–1450. doi:10.1001/jama.2015.2761
18. Li X, Zuo C, Lu W, et al. Evaluation of remote pharmacist-led outpatient service for geriatric patients on rivaroxaban for nonvalvular atrial fibrillation during the COVID-19 pandemic. *Front Pharmacol*. 2020;11:1275. doi:10.3389/fphar.2020.01275
19. Shiga T, Kimura T, Fukushima N, et al. Effects of a pharmacist-led educational interventional program on electronic monitoring-assessed adherence to direct oral anticoagulants: a randomized, controlled trial in patients with nonvalvular atrial fibrillation. *Clin Ther*. 2022;44(11):1494–1505. doi:10.1016/j.clinthera.2022.09.011
20. Wilson AS, Pham T, Mbusa D, et al. Pharmacist-led, checklist intervention did not improve adherence in ambulatory patients starting/resuming DOACs. *J Am Pharm Assoc*. 2023;63(3):878–884e3. doi:10.1016/j.japh.2023.02.019
21. Faul F, Erdfelder E, Buchner A, Lang AG. Statistical power analyses using G*Power 3.1: tests for correlation and regression analyses. *Behav Res Methods*. 2009;41(4):1149–1160. doi:10.3758/brm.41.4.1149
22. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175–191. doi:10.3758/bf03193146
23. Lin SY, Chen YW, Kang HC, et al. Effects of a pharmacist-managed anticoagulation outpatient clinic in Taiwan: evaluation of patient knowledge, satisfaction, and clinical outcomes. *Postgrad Med*. 2021;133(8):964–973. doi:10.1080/00325481.2021.1949212
24. Kripalani S, Risser J, Gatti ME, Jacobson TA. Development and evaluation of the Adherence to Refills and Medications Scale (ARMS) among low-literacy patients with chronic disease. *Value Health*. 2009;12(1):118–123. doi:10.1111/j.1524-4733.2008.00400.x
25. Huang YM, Wang T, Yang YM, Chang YH, Chan HY, Lin HW. Medication refills do not guarantee medication intake: translation and validation of the adherence to refills and medications scale in traditional Chinese among individuals with type 2 diabetes in Taiwan. *Postgrad Med*. 2025;137 (1):68–78. doi:10.1080/00325481.2024.2444258
26. Sentinel Initiative. Gastrointestinal bleeding algorithm defined in "Thromboembolic stroke, intracranial hemorrhage, gastrointestinal bleeding, and major extracranial bleeding following apixaban, dabigatran, and rivaroxaban use in patients aged 64 years and younger with atrial fibrillation: an inverse probability of treatment weighting analysis". Available from: https://www.sentinelinitiative.org/methods-data-tools/health-outcomes-interest/gastrointestinal-bleeding-algorithm-defined-1. Accessed August 18, 2025.
27. Sentinel Initiative. Intracranial hemorrhage algorithm defined in "Thromboembolic stroke, intracranial hemorrhage, gastrointestinal bleeding, and major extracranial bleeding following apixaban, dabigatran, and rivaroxaban use in patients aged 64 years and younger with atrial fibrillation: an inverse probability of treatment weighting analysis". Available from: https://www.sentinelinitiative.org/methods-data-tools/health-outcomes-interest/intracranial-hemorrhage-algorithm-defined-2. Accessed August 18, 2028.
28. Sentinel Initiative. Thromboembolic stroke algorithm defined in "Thromboembolic stroke, intracranial hemorrhage, gastrointestinal bleeding, and major extracranial bleeding following apixaban, dabigatran, and rivaroxaban use in patients aged 64 years and younger with atrial fibrillation: an inverse probability of treatment weighting analysis". Available from: https://www.sentinelinitiative.org/methods-data-tools/health-outcomes-interest/thromboembolic-stroke-algorithm-defined-2. Accessed August 18, 2025.
29. Lin SY, Tang SC, Kuo CH, et al. Impact of direct oral anticoagulant concentration on clinical outcomes in Asian patients with atrial fibrillation. *Clin Pharmacol Ther*. 2023;114(1):230–238. doi:10.1002/cpt.2927
30. Lin SY, Liu YB, Ho LT, et al. Impact of age and factor Xa inhibitor concentrations on bleeding risk in patients with atrial fibrillation. *Clin Pharmacol Ther*. 2025;118(1):156–163. doi:10.1002/cpt.3654
31. Steffel J, Collins R, Antz M, et al. 2021 European Heart Rhythm Association practical guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. *Europace*. 2021;23(10):1612–1676. doi:10.1093/europace/euab065
32. Milling TJ, Frontera J. Exploring indications for the Use of direct oral anticoagulants and the associated risks of major bleeding. *Am J Manag Care*. 2017;23(4 Suppl):S67–S80.
33. Toso E, Peyracchia M, Matta M, et al. Incidence of thromboembolic events following atrial fibrillation catheter ablation and rate control strategies according to the kind of oral anticoagulation: a systematic review and meta-analysis. *Int J Cardiol*. 2018;270:172–179. doi:10.1016/j.ijcard.2018.06.082
34. Eikelboom JW, Quinlan DJ, Hirsh J, Connolly SJ, Weitz JI. Laboratory monitoring of non-vitamin K antagonist oral anticoagulant use in patients with atrial fibrillation: a review. *JAMA Cardiol*. 2017;2(5):566–574. doi:10.1001/jamacardio.2017.0364
35. Lin SY, Kuo CH, Ho LT, et al. Association between apixaban concentration and clinical outcomes in Asians with atrial fibrillation. *Circ Arrhythm Electrophysiol*. 2022;15(5):e010693. doi:10.1161/circep.121.010693