# Are the Direct Oral Anticoagulants Better for Patients with Low Time in the Therapeutic Range on Vitamin K Antagonist Therapy?

Jordan K. Schaefer[1] Geoffrey D. Barnes[2]

[1] Division of Hematology/Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, United States
[2] Division of Cardiovascular Medicine, Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, United States

**Address for correspondence** Geoffrey D. Barnes, MD, MSc, 2800 Plymouth Rd B14 G214, Ann Arbor, MI 48108 (e-mail: gbarnes@med.umich.edu).

Thromb Haemost 2024;124:791–794.

## Introduction

The direct oral anticoagulants (DOACs: apixaban, dabigatran, edoxaban, and rivaroxaban) are first-line anticoagulants for many patients with nonvalvular atrial fibrillation (NVAF) and venous thromboembolism (VTE).[1,2] This is due to their efficacy, safety profile, ease of administration, lack of a routine laboratory monitoring, and limited food or drug interactions. The landmark clinical trials that led to their approval showed generally high rates of mediation adherence.[3] Of course, taking anticoagulants as directed (medication adherence) is critical to realizing the beneficial results seen in studies.[4] However, it is uncertain if the high rates of adherence seen in a clinical trial population will be realized in actual clinical practice. Specific to DOAC therapy, it is uncertain if patients with low time in the therapeutic range (TTR) and high levels of international normalized ratio (INR) variability while on vitamin K antagonist (VKA) therapy are better served by transitioning to a DOAC, in large part due to questions of medication adherence. There have been concerns that adherence and persistence may be lower in this group with mixed study results to date.[5–8]

In this issue of *Thrombosis and Haemostasis,* Elling et al reported a retrospective cohort study of 437 patients anticoagulated for any indication, switching from VKAs to DOACs from 2012 to 2019.[9] Medication adherence was evaluated by proportion of days covered by an anticoagulant prescription. Of this cohort, nearly 70% had VKA TTRs under 70%. However, this was not associated with subsequent good DOAC adherence (defined as >90% adherence), which was high for most patients (~80%). Poor INR control (low TTR, high time under the therapeutic range, or high INR variability) while on a VKA was also not associated with lower persistence on DOACs compared to patients with better INR control. The results suggest that poor INR control should not dissuade clinicians from transitioning patients from a VKA to a DOAC. However, the study has notable limitations, including the potential for confounding and misclassification.[9] These issues are common in studies relying on prescription claims or fill data. The study was also small and may not capture important subgroups. Finally, the reason for poor INR control is not well described.

## DOAC Adherence after VKA Therapy

Predicting or monitoring DOAC medication adherence is desirable clinically to prevent patients from experiencing the potentially devastating or even deadly consequences of inadequate anticoagulation. Most commonly, patients are anticoagulated for VTE and/or NVAF. Such patients could be anticipated to suffer pulmonary embolism and/or stroke in the setting of nonadherence, a risk that is likely proportional to the degree of thrombotic risk of the individual patient. DOACs relative to VKAs have (1) less routine laboratory monitoring, (2) different pharmacokinetics,[10,11] and (3) more challenges to access.[12] These factors could put patients at greater risk for or from nonadherence. Understanding these risk factors for anticoagulant nonadherence helps clinicians and patients select the most appropriate medication. Even if prior VKA control (as measured by a TTR) is not a good predictor of future DOAC adherence, clinicians and health systems may still want to offer closer follow-up and support for patients believed to be at risk for nonadherence. How best to identify those patients remains an area of important future investigation.

**received**
May 8, 2024
**accepted**
May 13, 2024
**article published online**
June 1, 2024


Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

**DOI** https://doi.org/10.1055/s-0044-1787299.
**ISSN** 0340-6245.

## The Advantage and Concern with Less Monitoring

The lack of routine laboratory monitoring is one of the most attractive features of the DOACs compared to VKAs. However, the laboratory and clinical follow-up required for INR monitoring provides an opportunity to monitor medication adherence that is not as easily accomplished with the DOACs. Patients may have less clinical follow-up by anticoagulation clinic or other clinicians when on DOAC therapy.[13]

Studies have shown mixed results when evaluating DOAC adherence—notable with variation by indication for anticoagulation, duration of time on anticoagulation, patient age, sex, and more.[9,10,14] There may be subgroups that are more or less adherent to anticoagulant therapy. The specific reason for poor INR control may also be a significant factor for certain patients but not others.[15] This hypothesis requires more investigation. For instance, patients with poor INR control due to variable vitamin K intake or dietary issues may do better on a DOAC without this same concern. Patients with poor INR control due to time, transportation, or other barriers to completing INR monitoring also may do better on a DOAC. Similar benefits have been seen when VKA-treated patients transition to home INR monitoring. In contrast, patients with poor INR control due to other reasons (e.g., missing medication doses) may continue to have poor adherence after changing to a DOAC.

DOAC drug levels,[13] refill patterns, and patient self-report are the primary tools to assess for DOAC adherence. If a patient experiences a breakthrough thrombotic event on a DOAC, nonadherence may be a potential explanation. Efforts to improve medication adherence, potentially through educational interventions or closer follow-up, should be prioritized, along with efforts to detect patients not adherent to DOACs.[16]

## DOAC versus VKA Pharmacokinetics

While it is suggested that 60 to 70% TTR is desirable for warfarin-treated patients to achieve optimal outcomes,[9,17] it is not clear what level of DOAC adherence is needed, or how this may differ between patients. It is notable that DOAC half-lives are 5 to 17 hours.[18] Missing one dose of a daily-dosed DOAC would result in <25% drug levels encountered the time the dose was next due; missing one dose of a twice-daily DOAC would result in <50% drug levels by the time the next dose was due. In contrast, VKAs often have a longer half-life (~40 hours for warfarin) and a missed dose may be less likely to be associated with low anticoagulant drug levels. Therefore, it is unclear if patients who occasionally miss doses of anticoagulant are better protected with longer half-life drugs.

Elling et al's study included the twice-daily anticoagulants apixaban and dabigatran, along with the daily rivaroxaban. Previous studies have shown that medication adherence may be better for once-daily dosing compared to twice daily.[19,20] However, comparative efficacy studies between the most commonly used DOACs, apixaban and rivaroxaban, remain limited.

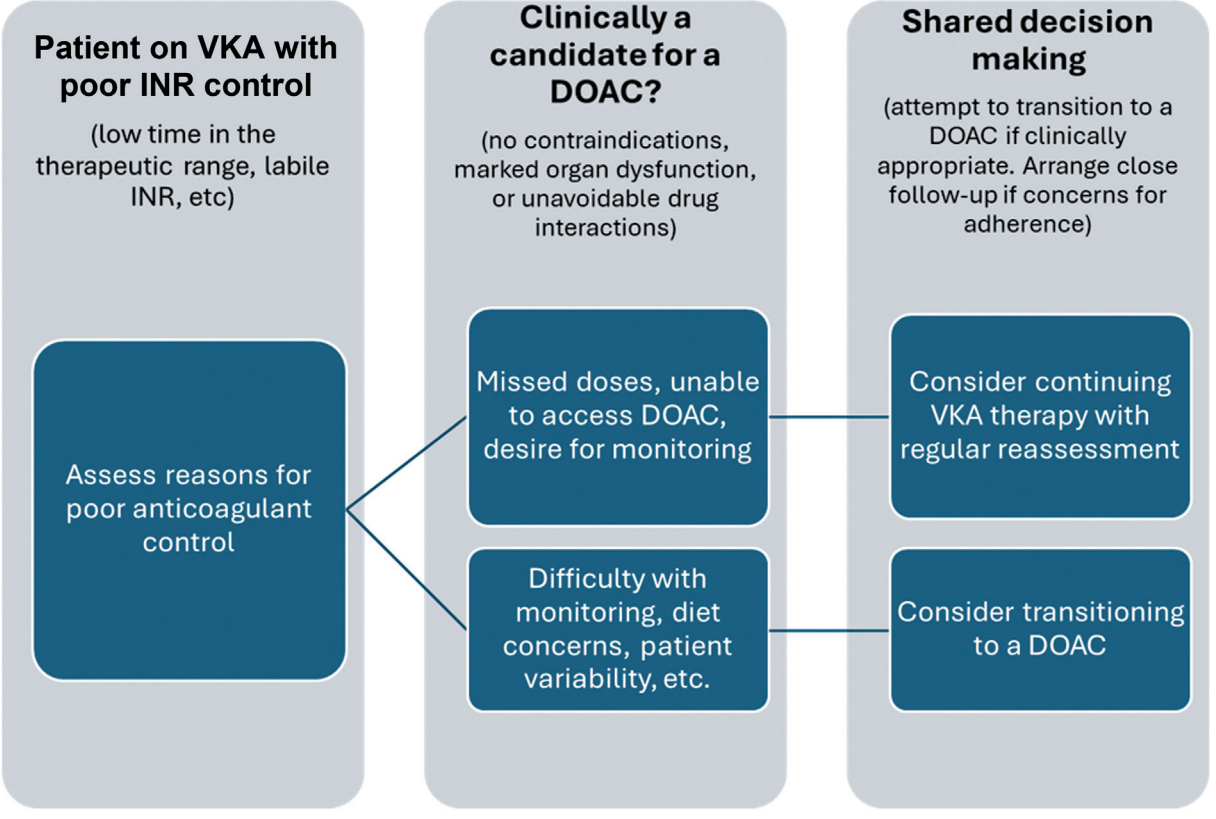


**Fig. 1** Approach to selecting oral anticoagulant therapy for patients with poor INR control.

 

## Drug Access

Sociodemographic factors are another important influence of medication persistence and adherence. Historically disadvantaged populations in the United States are less likely to switch to a DOAC.[21] This is partially driven by cost and/or medication access issues.[22] While not applicable to all patients, health systems, or countries, it is an important consideration for many patients considering VKA to DOAC transition.

## Should Patients with Poor INR Control Be Changed to DOACs?

The available data seem to suggest that in general, DOACs may be appropriate for patients with poor INR control. However, further research should confirm this hypothesis, especially in key patient subgroups. Until such data are available, the approach outlined in the figure (►**Fig. 1**) may be reasonable. It is important to engage patients and the entire health care team to try to optimize adherence as a part of anticoagulant stewardship. Barriers and facilitators of nonadherence should be identified. Clinicians, nurses, pharmacists, and social workers all play an important role in promoting anticoagulant adherence and should assess adherence in patient interactions.

Finally, oral anticoagulation is but one pillar of the holistic or integrated care management of many chronic long-term conditions, such as NVAF. Indeed, current guidelines promote such a holistic management approach.[23] Even then, adherence to such integrated care impacts on overall prognosis in patients with NVAF.[24,25] Hence, assessment of adherence should not only extend to drugs, but also to the overall holistic management plan, to improve outcomes in our patients.

Conflict of Interest
J.K.S. received consulting fees from Pfizer, Sanofi. G.D.B. received grant funding from Boston Scientific; Consulting: Pfizer, Bristol-Myers Squibb, Janssen, Bayer, AstraZeneca, Sanofi, Anthos, Abbott Vascular, Boston Scientific; He also is a member of Board of Directors for Anticoagulation Forum.

### References

1 Joglar JA, Chung MK, Armbruster AL, et al; Peer Review Committee Members. 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2024;149(01): e1–e156
2 Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020;4(19):4693–4738
3 Rodriguez RA, Carrier M, Wells PS. Non-adherence to new oral anticoagulants: a reason for concern during long-term anticoagulation? J Thromb Haemost 2013;11(02):390–394
4 Osterberg L, Blaschke T. Adherence to medication. N Engl J Med 2005;353(05):487–497
5 Pundi KN, Perino AC, Fan J, et al. Direct oral anticoagulant adherence of patients with atrial fibrillation transitioned from warfarin. J Am Heart Assoc 2021;10(23):e020904
6 Toorop MMA, Chen Q, Kruip MJHA, et al. Switching from vitamin K antagonists to direct oral anticoagulants in non-valvular atrial fibrillation patients: does low time in therapeutic range affect persistence? J Thromb Haemost 2022;20(02):339–352
7 Solla-Ruiz I, Villanueva-Benito I, Paredes-Galán E, et al. Differences between patient-driven adherence to vitamin K antagonists and direct oral anticoagulants. Do few missed doses matter? ACO-MEMS Study. Thromb Res 2019;179:20–27
8 Bartoli-Abdou JK, Patel JP, Vadher B, et al. Long-term adherence to direct acting oral anticoagulants and the influence of health beliefs after switching from vitamin-K antagonists: findings from the Switching Study. Thromb Res 2021;208:162–169
9 Elling T, Hak E, Bos JH, Tichelaar VYIG, Veeger NJGM, Meijer K. Effect of previous INR control during VKA therapy on subsequent DOAC adherence and persistence, in patients switched from VKA to DOAC. Thromb Haemost 2024;124(08):778–790
10 van der Horst SFB, de Vries TAC, Chu G, et al. Prevalence and predictors of nonadherence to direct oral anticoagulant treatment in patients with atrial fibrillation. TH Open 2023;7(03): e270–e279
11 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(03):e005969
12 Tarn DM, Shih KJ, Schwartz JB. Reasons for nonadherence to the direct oral anticoagulant apixaban for atrial fibrillation. J Am Geriatr Soc 2021;69(12):3683–3687
13 Conway SE, Hwang AY, Ponte CD, Gums JG. Laboratory and clinical monitoring of direct acting oral anticoagulants: what clinicians need to know. Pharmacotherapy 2017;37(02):236–248
14 Charlton A, Vidal X, Sabaté M, Bailarín E, Martínez LML, Ibáñez L. Factors associated with primary nonadherence to newly initiated direct oral anticoagulants in patients with nonvalvular atrial fibrillation. J Manag Care Spec Pharm 2021;27(09):1210–1220
15 Witt DM, Clark NP, Kaatz S, Schnurr T, Ansell JE. Guidance for the practical management of warfarin therapy in the treatment of venous thromboembolism. J Thromb Thrombolysis 2016;41(01): 187–205
16 Sylvester KW, Ting C, Lewin A, et al. Expanding anticoagulation management services to include direct oral anticoagulants. J Thromb Thrombolysis 2018;45(02):274–280
17 Gateman D, Trojnar ME, Agarwal G. Time in therapeutic range: warfarin anticoagulation for atrial fibrillation in a community-based practice. Can Fam Physician 2017;63(10):e425–e431
18 Schaefer JK, Elshoury A, Nachar VR, Streiff MB, Lim MY. How to choose an appropriate anticoagulant for cancer-associated thrombosis. J Natl Compr Canc Netw 2021;19(10):1203–1210
19 McHorney CA, Crivera C, Laliberté F, Germain G, Wynant W, Lefebvre P. Adherence to rivaroxaban versus apixaban among patients with non-valvular atrial fibrillation: analysis of overall population and subgroups of prior oral anticoagulant users. PLoS One 2018;13(04):e0194099
20 Ingason AB, Hreinsson JP, Lund SH, et al. Comparison of medication adherence to different oral anticoagulants: population-based cohort study. BMJ Open 2023;13(01):e065700
21 Schaefer JK, Sood SL, Haymart B, et al. Sociodemographic factors in patients continuing warfarin vs those transitioning to direct oral anticoagulants. Blood Adv 2017;1(26):2536–2540
22 Tarn DM, Shih K, Tseng C-h, Thomas A, Schwartz JB. Reasons for nonadherence to the direct oral anticoagulant apixaban. JACC Adv 2023;2(01):100175

 

23 Chao TF, Joung B, Takahashi Y, et al. 2021 focused update consensus guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: Executive Summary. Thromb Haemost 2022;122(01):20–47
24 Treewaree S, Lip GYH, Krittayaphong R. Non-vitamin K antagonist oral anticoagulant, warfarin, and ABC pathway adherence on hierarchical outcomes: win ratio analysis of the COOL-AF registry. Thromb Haemost 2024;124(01):69–79
25 Romiti GF, Pastori D, Rivera-Caravaca JM, et al. Adherence to the 'Atrial Fibrillation Better Care' pathway in patients with atrial fibrillation: impact on clinical outcomes-a systematic review and meta-analysis of 285,000 patients. Thromb Haemost 2022;122(03):406–414