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COMMENTARY

Are outpatient anticoagulation management services the wave of the future (again)?

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When the first direct oral anticoagulants (DOACs) were Food and Drug Administration-approved and made available for clinical use in the treatment of venous thromboembolism (VTE) and stroke prevention of atrial fibrillation, the excitement over options that required neither routine monitoring nor frequent dose adjustments was felt by prescribers and patients alike. Although much has been learned about DOACs since then, the enthusiasm for these features has not dimmed. Apixaban, the most widely used DOAC, was ranked the 52nd most commonly prescribed drug in 2019 according to www.clincalc.com. More than 14 million prescriptions were filled for more than 3 million patients during that year. DOACs continue to be celebrated for greater convenience and, in some cases, greater safety over vitamin K antagonists (VKAs).

In their recent paper, Sylvester et al.[1] report on their successful experience managing DOACs using an outpatient anticoagulation management service (AMS). The original model for the outpatient AMS was designed to facilitate the frequent monitoring and nuanced dose adjustments necessary to optimize effectiveness and minimize bleeding in patients using VKAs.[2] Such services were demonstrated to be cost effective, simultaneously adding quality adjusted life years and reducing cost of care due, at least in part, to a reduction in strokes (ischemic or hemorrhagic) and other embolic events.[3,4] Many of these benefits were presumed to be directly linked to increased time in therapeutic range, a metric not monitored in the use of DOACs because of generally reliable pharmacokinetics. However, even in the absence of a need for frequent dose adjustments DOACs remain high-risk medications and are vulnerable to dosing errors, medication interactions and variability from renal and hepatic function as well as absorption. According to Sylvester et al,[1] rationale for using AMS for DOAC patients include safer and more effective transitions of care and reduced provider burnout. Specific services provided for DOAC patients include dose adjustments, procedure planning, assessment of adherence, assessment for bleeding/recurrent thromboembolism, side effects, new medications/interactions, and periodic laboratory assessment for changes in renal or liver function. Such services not only improve patient care but can serve to reduce burden on an already overburdened health care system, particularly in the wake of the SARS-CoV-2 pandemic. Over a 4-year period, the pharmacist-run Brigham and Women's Hospital AMS saw 1622 patients in 3154 follow-up visits, which may otherwise have occurred in busy primary care and cardiology clinics further increasing the already long wait times for such clinics. The comprehensive AMS also provided regular chart review (every 3 months during active surveillance) to capture changes in clinical status that might be missed when patients are otherwise only seen every 6–12 months by the referring physician.

Uses for DOACs are broad and include not only stroke prevention in atrial fibrillation and treatment of VTE but also VTE-prophylaxis in orthopedic surgical patients[5,6] and hospitalized patients,[7] treatment of cancer-associated thrombosis,[8-10] and prevention of ischemic events after percutaneous coronary intervention in the setting of atrial fibrillation.[11] Additional data on reduced dosing approaches

TABLE 1 FDA-approved/guideline driven doses and indications for DOACs in adult patients

Drug and dose	Indication
Apixaban 10 mg BID	Initial treatment of VTE (first 7 days)
	Initial treatment of cancer-associated VTE (first 7 days)
Apixaban 5 mg BID	Acute treatment of VTE (after 7 days of 10 mg BID)
	Acute treatment of cancer-associated VTE (after 7 days of 10 mg BID)
	Long-term anticoagulation/secondary prevention of VTE
	Nonvalvular atrial fibrillation
	Post-PCI in atrial fibrillation
Apixaban 2.5 mg BID	VTE prophylaxis after orthopedic surgery
	Long-term anticoagulation/secondary prevention of VTE after 6 months of therapeutic treatment
	Nonvalvular atrial fibrillation with 2 of the following: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dl
	Post-PCI in atrial fibrillation with 2 of the following: age ≥80 years, body weight ≤60 kg, serum creatinine ≥1.5 mg/dl
Rivaroxaban 15 mg[a] BID	Initial treatment of VTE (first 21 days)
	Initial treatment of cancer-associated VTE (first 21 days)
Rivaroxaban 20 mg[a] daily	Acute treatment of VTE (after 21 days of 15 mg BID)
	Acute treatment of cancer-associated VTE (first 21 days)
	Long-term anticoagulation/secondary prevention of VTE
	Nonvalvular atrial fibrillation (CrCl >50 ml/min)
Rivaroxaban 15 mg[a] daily	Nonvalvular atrial fibrillation (CrCl ≤50 ml/min)
Rivaroxaban 10 mg daily	Long-term anticoagulation/secondary prevention of VTE after 6 months of therapeutic treatment
	VTE prophylaxis in acutely ill medical patients (duration 31–39 days)
	VTE prophylaxis postorthopedic surgery
Rivaroxaban 2.5 mg BID	Stable coronary artery disease/peripheral artery disease in combination with aspirin (75–100 mg)
Edoxaban 60 mg daily	Acute treatment of VTE (after 5 days of parenteral anticoagulation)
	Acute treatment of cancer-associated VTE (after 5 days of parenteral anticoagulation)
	Long-term anticoagulation/secondary prevention of VTE
	Nonvalvular atrial fibrillation (CrCl >50 to 95 ml/min)
	Postpercutaneous coronary intervention with stent placement + atrial fibrillation with clopidogrel ± aspirin
Edoxaban 30 mg daily	Acute treatment of VTE (after 5 days of parenteral anticoagulation), patient weight ≤60 kg, OR CrCl 15–50 ml/min
	Nonvalvular atrial fibrillation (CrCl 15–50 ml/min)
	Nonvalvular atrial fibrillation in adult ≥60 years and one of the following: weight ≤60 kg, concomitant use of potent P-glycoprotein inhibitor, CrCl 30–50 ml/min
Edoxaban 15 mg daily	Nonvalvular atrial fibrillation in adult ≥80 years with weight ≤45 kg OR weight ≤60 kg and one of the following: history of GI bleeding or bleeding from a critical area, continuous use of a nonsteroidal anti-inflammatory drug, CrCl <30 ml/min
Dabigatran 220 mg daily	VTE prophylaxis postorthopedic surgery (10–35 days)
Dabigatran 150 mg BID	Acute treatment of VTE (after 5 days of parenteral anticoagulation)
	Long-term anticoagulation/secondary prevention of VTE
	Nonvalvular atrial fibrillation, CrCl >30 ml/min
	Postpercutaneous coronary intervention with stent placement + nonvalvular atrial fibrillation with clopidogrel ± aspirin
Dabigatran 110 mg BID	Postpercutaneous coronary intervention with stent placement + nonvalvular atrial fibrillation with clopidogrel ± aspirin
Dabigatran 75 mg BID	Nonvalvular atrial fibrillation CrCl 15 to ≤30 ml/min

Abbreviations: BID, twice per day; CrCl, creatinine clearance; PCI, percutaneous coronary intervention; VTE, venous thromboembolism

[a]Must be taken with food.

are available for extended prophylaxis in patients who have received 6–12 months of therapy for acute VTE.[12,13] Table 1 includes a near-exhaustive list of Food and Drug Administration-approved and/or guideline driven indications and dosing recommendations for various DOACs in the modern age, an important reminder that although DOACs may seem "easier" and/or "simpler," their use is ever evolving and actually still quite complex for patients at extremes of age, weight, and renal function.

With added indications and dosing nuances comes increased complexity, a greater diversity of prescribers and increased risk of medication errors, drug-drug interactions, and adverse events. Despite this, in the absence of a need for regular monitoring and dose adjustments, many patients and providers may not have access to AMS or feel they are not necessary.

However, Sylvester et al are not the only group to establish and report on the outcomes of pharmacist-led DOAC management services. An analogous clinic was established in Newfoundland and Labrador, Canada, with similar findings, including 51 medication issues identified in 74 clinic visits for 47 patients.[14] In institutions without an AMS and/or who have already scaled back an AMS initially designed to manage VKAs, there may still be resistance by patients, providers and institutions, to (re)expanding such services. In their experience, Sylvester et al report that referring physicians identified a few reservations to the AMS DOAC clinic including the work required to submit a referral and not recognizing the value of services provided. Institutions may object to financially investing in services which might result in few and/or low-billing encounters when many physicians have already incorporated prescribing DOACs into their workflow at no additional cost above and beyond their salaries. Patients may object to trying to incorporate yet another appointment into already busy schedules.

For these reasons, it may be ultimately be more practical to identify specific, at-risk populations of patients using DOACs for enrollment in such services. Potential candidate populations to target may include the following:

1. *Cancer patients*: drug-drug interactions for DOACs include a number of drugs used with increased frequency and complexity in the cancer population, such as chemotherapeutic agents, antifungals, immunosuppressive agents, and antiepileptic drugs.[15] Additionally, cancer patients experience altered absorption, chemotherapy-induced nausea and vomiting and baseline elevations in bleeding and thrombosis risk.[16]
2. *Patients at risk for nonadherence*: issues with adherence, particularly with regard to timing of doses, are common with DOAC therapy[17] and are associated with worse clinical outcomes.[18,19] Particularly in the atrial fibrillation population, a number of risk factors for nonadherence are known, including but not limited to age, comorbidities and health literacy.[20] The cost of DOACs is another important barrier to adherence, one which an AMS may help to alleviate by assisting navigation through insurance and drug access programs.
3. *Patients with variable or borderline renal and hepatic function*: patients with low renal function or at risk for changes are more likely to require changes to dosing or changing of agents entirely and warrant closer monitoring. Although not always a strict contraindication to DOAC use, patients with early stage hepatic impairment (Child-Pugh class A or B) are at higher risk for adverse outcomes and warrant additional monitoring/closer follow-up.
4. *Patients on multiple medications*: drug-drug interactions, although fewer, pose a danger to patients on DOACs much as they did for VKA users.[21] Furthermore, patients on multiple medications are at greater risk of medication errors.[22] Although routine monitoring of anti-factorXa (anti-Xa) or drug levels is not necessary for the majority of patients using DOACs, checking levels may be helpful in patients on medications with potential to alter drug metabolism.[23] An AMS well-versed in testing, with expert knowledge on available assays and timing of their conduct, may be best equipped to arrange and interpret such testing.

We recognize that many providers, particularly those in smaller community settings but even some in major hospitals, may not have access to a pre-built AMS. Although starting a new one from scratch will undoubtedly be a greater undertaking than simply expanding existing services, it may be worthwhile in certain settings such as cancer centers or those with high proportions of medically complex patients. Although cost-effectiveness data, such as we have for VKA patients, is lacking for the DOAC population a reduction in provider burnout/turnover as well as admissions and readmissions for anticoagulation-related complications may ultimately prove cost-effective.

To conclude, patients taking DOACs may benefit from the services of an AMS, and wider, integrated use of such services in combination with other supports, has the potential to reduce clinician/physician burnout. Prescribers may wish to start their referrals with the highest risk patients. Once potential benefits are realized a wider referral strategy and expansion (or reexpansion of services cut since a reduction in VKA use) may very well be in our future.

AUTHOR CONTRIBUTIONS

B.T.S.B conceived of, wrote and edited the manuscript and accepts responsibility to submit for publication.

RELATIONSHIP DISCLOSURE

B.T.S.B. reports no conflicts of interest for this manuscript.

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REFERENCES

1. Sylvester KW, Chen A, Lewin A, Fanikos J, Goldhaber SZ, Connors JM. Optimization of DOAC management services in a centralized anticoagulation clinic. *Res Pract Thromb Haemost*. 2022;6(3). doi:10.1002/rth2.12696

2. Mohammad I, Korkis B, Garwood CL. Incorporating comprehensive management of direct oral anticoagulants into anticoagulation clinics. *Pharmacotherapy*. 2017;37(10):1284-1297. doi:10.1002/phar.1991
3. Sullivan PW, Arant TW, Ellis SL, Ulrich H. The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US. *Pharmacoeconomics*. 2006;24(10):1021-1033. doi:10.2165/00019053-200624100-00009
4. Chua WB, Cheen HH, Kong MC, Chen LL, Wee HL. Modelling the cost-effectiveness of pharmacist-managed anticoagulation service for older adults with atrial fibrillation in Singapore. *Int J Clin Pharm*. 2016;38(5):1230-1240. doi:10.1007/s11096-016-0357-7
5. Samama CM, Laporte S, Rosencher N, et al. Rivaroxaban or enoxaparin in nonmajor orthopedic surgery. *N Engl J Med*. 2020;382(20):1916-1925. doi:10.1056/nejmoa1913808
6. Lassen MRR, Gary E, Gallus A, Pineo G, Chen D, Hornick P. Apixaban versus enoxaparin for thromboprophylaxis after knee replacement (ADVANCE-2): a randomised double-blind trial. *Lancet*. 2010;375(9717):807-815. doi:10.1016/S0140-6736(09)62125-5
7. Cohen AT, Harrington RA, Goldhaber SZ, et al. Extended thromboprophylaxis with betrixaban in acutely ill medical patients. *N Engl J Med*. 2016;375(6):534-544. doi:10.1056/nejmoa1601747
8. Agnelli G, Becattini C, Meyer G, et al. Apixaban for the treatment of venous thromboembolism associated with cancer. *N Engl J Med*. 2020;382(17):1599-1607. doi:10.1056/nejmoa1915103
9. Raskob GE, Van Es N, Verhamme P, et al. Edoxaban for the treatment of cancer-associated venous thromboembolism. *N Engl J Med*. 2018;378(7):615-624. doi:10.1056/nejmoa1711948
10. Young AM, Marshall A, Thirlwall J, et al. Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D). *J Clin Oncol*. 2018;36(20):2017-2023. doi:10.1200/jco.2018.78.8034
11. Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC expert consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease: a report of the American College of Cardiology Solution Set Oversight Committee. *J Am Coll Cardiol*. 2021;77(5):629-658. doi:10.1016/j.jacc.2020.09.011
12. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med*. 2013;368(8):699-708. doi:10.1056/nejmoa1207541
13. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376(13):1211-1222. doi:10.1056/nejmoa1700518
14. Hache J, Bonsu KO, Chitsike R, Nguyen H, Young S. Assessment of a pharmacist-led direct oral anticoagulant monitoring clinic. *Can J Hosp Pharm*. 2021;74(1):7-14.
15. Short NJ, Connors JM. New oral anticoagulants and the cancer patient. *Oncologist*. 2014;19(1):82-93. doi:10.1634/theoncologist.2013-0239
16. Sebuhyan M, Crichi B, Abdallah NA, et al. Drug-drug interaction (DDI) with direct oral anticoagulant (DOAC) in patients with cancer. *J Med Vasc*. 2020;45(6S):6S31-6S38. doi:10.1016/S2542-4513(20)30517-4
17. Talana AS, Huber K, Sorin M, Stalvey C, Davis K, Dietrich E. Patient-level adherence and interventions in an interdisciplinary DOAC clinic. *Thromb Res*. 2019;179:34-36. doi:10.1016/j.thromres.2019.04.021
18. Ozaki AF, Choi AS, Le QT, et al. Real-world adherence and persistence to direct oral anticoagulants in patients with atrial fibrillation. *Circ Cardiovasc Qual Outcomes*. 2020;13(3):e005969. doi:10.1161/circoutcomes.119.005969
19. Yamashiro K, Kurita N, Tanaka R, et al. Adequate adherence to direct oral anticoagulant is associated with reduced ischemic stroke severity in patients with atrial fibrillation. *J Stroke Cerebrovasc Dis*. 2019;28(6):1773-1780. doi:10.1016/j.jstrokecerebrovasdis.2018.09.019
20. Reading SR, Black MH, Singer DE, et al. Risk factors for medication non-adherence among atrial fibrillation patients. *BMC Cardiovasc Disord*. 2019;19(1): doi:10.1186/s12872-019-1019-1
21. Wiggins BS, Dixon DL, Neyens RR, Page RL 2nd, Gluckman TJ. Select drug-drug interactions with direct oral anticoagulants: JACC review topic of the week. *J Am Coll Cardiol*. 2020;75(11):1341-1350. doi:10.1016/j.jacc.2019.12.068
22. Walsh CA, Bennett KE, Wallace E, Cahir C. Identifying adherence patterns across multiple medications and their association with health outcomes in older community-dwelling adults with multimorbidity. *Value Health*. 2020;23(8):1063-1071. doi:10.1016/j.jval.2020.03.016
23. Douxfils J, Ageno W, Samama CM, et al. Laboratory testing in patients treated with direct oral anticoagulants: a practical guide for clinicians. *J Thromb Haemost*. 2018;16(2):209-219. doi:10.1111/jth.13912

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