Role of the anticoagulant monitoring service in 2018: beyond warfarin

Nathan P. Clark

Kaiser Permanente Colorado, Aurora, CO; and Department of Clinical Pharmacy, Colorado University Skaggs School of Pharmacy and Pharmaceutical Sciences, Aurora, CO

The direct oral anticoagulants (DOACs) have a wide therapeutic index, few drug interaction, no dietary interactions and do not require dose adjustment according to the results of routine coagulation testing. Despite these advantages over warfarin, the DOACs remain high risk medications. There is evidence that non-adherence, off-label dosing and inadequate care transitions during DOAC therapy increase the risk of bleeding and thromboembolic complications. Although DOACs are approved for a growing number of indications, there remain patient populations who are not good candidates. Existing expertise within an Anticoagulation Management Service (AMS) should be leveraged to optimize all anticoagulant therapies including the DOACs. The AMS can facilitate initial drug therapy selection and dose management, reinforce patient education and adherence as well as managing drug interactions and invasive procedures. In the event that a transition to warfarin is warranted, the AMS is already engaged which limits the risk of fragmented patient care and ensures that therapeutic anticoagulation is re-established in a timely manner. The AMS of the future will provide comprehensive management for all patients receiving anticoagulant medications and continue to provide anticoagulation expertise to the healthcare team.

Learning Objectives

- Describe quality improvement opportunities in the use of direct oral anticoagulants
- Describe interventions an Anticoagulation Management Service may engage in to promote safe and effective use of direct oral anticoagulants

Introduction

The centralized anticoagulation management service (AMS) has been an important element for optimized anticoagulation care delivery of traditional anticoagulants in both inpatient and ambulatory care settings.[1,2] Although studies comparing anticoagulation outcomes between the AMS and usual care have demonstrated mixed results, a centralized system of care provides several practical advantages, including gains in consistency and efficiency of care delivery.[3-6] Observational studies have described significant increases in time in therapeutic range (TTR) and reduction in bleeding, thromboembolic, and fatal outcomes compared with usual care.[3] In addition, residing in a country where vitamin K antagonists are predominantly managed by an AMS was a significant predictor of TTR in post hoc analysis of the ARISTOTLE trial, which compared warfarin and apixaban in atrial fibrillation (AF).[7] The Anticoagulation Forum recommends patients be managed within an AMS in its clinical guidance on delivery of optimal anticoagulant care.[1,2]

Compared with warfarin, direct-acting oral anticoagulants (DOACs) have a wider therapeutic index, few clinically important drug interactions, and no known dietary interactions.[8] In addition, DOACs have conventional dosing, and there are no routine coagulation tests required to adjust medication doses.[9-12] However, like warfarin, DOACs are high-risk medications, and incorporating DOAC management into an AMS may help us to fully realize the benefit of this class of medications.[13]

Shehab et al[14] at the Centers for Disease Control analyzed characteristics of emergency department visits for adverse drug events (ADEs) in the United States from 2005 to 2006 and 2013 to 2014. The analysis included 42 585 cases from 58 emergency departments participating in the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance Project. Anticoagulants remain the drug class most frequently associated with adverse drug events in the DOAC era, and the rate of anticoagulant-related ADEs seems to be increasing.[14] Anticoagulants resulted in 7.3% of emergency department visits for ADEs from 2005 to 2006, and that rate more than doubled 3 years after DOACs were introduced.[14] This could be explained by greater use of anticoagulants or enhanced case identification. However, the growth rate of anticoagulant ADE reporting has substantially outpaced growth in anticoagulant use.[15] The Institute for Safe Medical Practice found anticoagulants continue to be implicated in a significant number of medication-related injuries (n = 18 978) and deaths (n = 3018) in its analysis of 2016 data from the US Food and Drug Administration Adverse Event Reporting System.[16] The most commonly reported agents were rivaroxaban (68.4%) and apixaban (14.3%), followed by dabigatran (8.8%), warfarin (8%), and edoxaban (<1%).[16]

Almost 80% of ADEs related to anticoagulants were hemorrhages in the Centers for Disease Control report.[14] The report likely does

Conflict-of-interest disclosure: The author declares no competing financial interests.

Off-label drug use: None disclosed.

not capture the number of patients with thrombosis resulting from nonadherence. Complications related to the absence of anticoagulant activity are not traditionally classified as ADEs, because they are related to absence of drug. Understanding the burden of avoidable thrombosis is critical, because these complications are more often life threatening than bleeding. This is a significant gap in our understanding of the potential limitations of more expensive anticoagulants that have short half-lives and limited routine follow-up to assess adherence in a real-world population.

Whether the AMS can help us realize the full potential of DOACs remains to be seen. This article will discuss several core activities the AMS can support in optimizing the use of DOACs.

Anticoagulant therapy initiation

Confirm appropriate indication

The first step in high-quality anticoagulation care delivery is to confirm anticoagulation is indicated. The AMS can be an important double check to confirm patients with AF have sufficient risk of stroke (ie, $CHADS_2$-VASc ≥ 1) and to confirm objective diagnosis of deep vein thrombosis or pulmonary embolism, deep vs superficial vein thrombosis, or appropriate indication for venous thromboembolism (VTE) prophylaxis. An analysis of the PINNACLE (Practice Innovation and Clinical Excellence) Registry of the National Cardiovascular Data Registry investigated the use of oral anticoagulants in patients with AF and low risk of stroke between 1 January 2008 and 30 December 2012.[17] Among patients with AF and a $CHADS_2$ score of 0 or CHA_2DS_2-VASc score of 0, oral anticoagulants were prescribed in 23.3% and 26.6%, respectively.[17] These findings would suggest there a quality improvement opportunity in avoiding anticoagulation in patients without a compelling indication. It is likely that DOACs have lowered the threshold for anticoagulation initiation, which may predispose to overuse of anticoagulants, which has not historically been a concern with warfarin. The AMS can also facilitate consults with clinical colleagues in cases where a prescription is written for a patient without a usual indication for a DOAC.

Selecting the optimal anticoagulant

Randomized controlled trials support the use of DOACs for a growing list of indications, and several guidelines support the use of DOACs in preference to warfarin for management of VTE and AF.[18-20] However, there are still some patients for whom warfarin remains the preferred anticoagulant, because of either limited evidence for DOACs, pharmacokinetic interference, or evidence of treatment failure (eg, mechanical heart valves).[8] Ideally, criteria for anticoagulant selection are developed by local content experts within the health care system and in collaboration with AMS leadership and consistent with the best available evidence. The criteria should be updated annually as a part of AMS policy and procedure or as new indications or evidence from clinical trials becomes available.

The individual drugs making up the DOAC class also have subtle differences. In-depth knowledge of these properties can assist providers in selecting the optimal DOAC for a specific patient. Again, a consistent policy directing the use of specific DOACs should facilitate consistent and high-quality anticoagulant care delivery. Medication characteristics that might be considered during DOAC selection include once daily vs twice daily dosing, use of a pill box, ability to crush the medication, cancer diagnosis, renal insufficiency, and history of gastrointestinal bleeding. In many cases, there are also drug formulary and insurance coverage considerations in drug therapy selection. Having dedicated anticoagulation specialists with in-depth clinical knowledge of DOACs as well as practical experience in navigating local benefit issues may help to streamline care decisions.

Anticoagulant initiation and dosing

The ORBIT-AF registry, a national prospective data set of US patients with AF, was leveraged to investigate the influence of real-world DOAC prescribing on patient outcomes.[21] Patients were categorized as either receiving DOAC doses consistent with US package labeling, being overdosed, or being underdosed. There were 721 patients excluded from the analysis (12.7%) because no renal function testing was available to inform dose selection. In addition, 1 in 8 patients received a DOAC dose either above or below the labeled dose. Perhaps unsurprisingly, underdosing (9.4%) was more common than overdosing (3.4%); underdosing was associated with an increased risk of cardiovascular hospitalization, and overdosing was associated with excess all-cause mortality.[21]

To enable precise DOAC dosing, the AMS should ensure appropriate baseline laboratory values are drawn and appropriately referenced to guide drug therapy decisions. At minimum, this includes serum creatinine and a complete blood count.[22,23] Additional labs, including liver function tests and baseline coagulation parameters such as the international normalized ratio (INR) and activated partial thromboplastin time, may be considered.[23]

The standard therapeutic DOAC dose is used for patients with AF and normal body weight and renal function.[9-12] Lower doses are recommended with decreasing renal function for dabigatran (creatine clearance [CrCL] <30 mL/min), rivaroxaban (CrCL 15-50 mL/min), and edoxaban (CrCL 15-50 mL/min).[9,10,12] Patients with 2 of 3 of either age ≥ 80 years, weight ≤ 60 kg, or serum creatinine ≥ 1.5 mg/dL receive a reduced dose of apixaban.[11] There are limited outcome data for use of DOACs in severe renal impairment (CrCL <30 mL/min); therefore, they are not typically recommended in this setting.[8] However, there is developing evidence that apixaban, the DOAC least reliant upon renal elimination, may be acceptable for use in patients with advanced renal disease.[24,25] Edoxaban is also contraindicated in patients with CrCL >95 mL/min because of excess stroke compared with warfarin in this subset of patients.[12]

Treatment of acute VTE is somewhat more complex than that of AF. Edoxaban and dabigatran require an initial 5 days of heparin or low molecular weight heparin before switching to the DOAC, whereas rivaroxaban and apixaban do not require heparin but have an initial period of higher oral dosing.[9-12] The AMS can play a critical role at high-risk junctures of DOAC therapy for VTE; specifically by confirming switching from parenteral anticoagulation (rather than overlap) to oral dabigatran or edoxaban. For the oral VTE options, the change from twice daily to once daily rivaroxaban at day 22 of treatment is an important time to check in with the patient and confirm dosing instructions.

Patient education

Effective drug therapy education is critical for all medications, and the Joint Commission highlights that anticoagulation patient education should include the need for ongoing monitoring, adherence, drug-food interactions (for warfarin), drug-drug interactions, and the potential for adverse effects.[26] Informed patients are more engaged in their health care, have better outcomes, and have reduced cost of care.[27] Unfortunately, the complexities of reliably providing

thorough education are often overlooked. Providing successful education to a population of patients with varying cultural backgrounds, educational levels, beliefs, and numeracy and literacy levels is challenging. Patient education as a 1-time event is not sufficient, and hospital discharge is not the optimal time for it to be provided. A prospective cohort of patients age ≥65 years hospitalized for acute coronary syndrome, heart failure, or pneumonia found that 40% were unable to accurately describe the reason for hospitalization, and more than half could not precisely describe plans for their follow-up appointment.[28]

The AMS is in the ideal position to reinforce anticoagulation patient education during longitudinal follow-up. In addition to reviewing medication instructions verbally, the AMS should develop written materials as well as videos or directions to online video content such as that made available by the Agency for Healthcare Research and Quality.

Long-term anticoagulation follow-up

There are no established guidelines for the recommended follow-up intervals for patients requiring long-term DOAC treatment. In general, it is advisable to check in within the first 2 weeks after DOAC initiation to ensure the patient is tolerating therapy based on the timing of transitions (eg, on the day of transition from parenteral to oral anticoagulation or dose reduction). This may be particularly important with dabigatran, where dyspepsia can be a bothersome but manageable adverse effect.[9] Beyond the first month of treatment, renal function must be assessed at least annually and potentially more frequently for patients with compromised or variable renal function and those receiving nephrotoxic chemotherapy.[8]

Longitudinal anticoagulant dose management

Among patients with AF, DOAC dose changes are only needed in the event of a reduction in renal function for edoxaban, dabigatran, and rivaroxaban or if additional dose reduction criteria are met for apixaban.[9-12] In addition, there are suggested dose reductions for patients receiving edoxaban or dabigatran with borderline renal insufficiency and P-glycoprotein (P-gp) inhibitor drug interactions.[9-12]

The AMS can facilitate duration of therapy assessment in a consistent manner for patients anticoagulated for VTE. Among patients for whom long-term anticoagulation is continued, the AMS can direct selection of the appropriate DOAC and dosing regimen. For dabigatran and edoxaban, there is only a single option, which is the same for management of acute and extended secondary VTE treatment.[9-12] Apixaban and rivaroxaban have 2 dosing options.[10,11] The usual treatment dose may be continued beyond 6 months, or the dose may be reduced to a prophylactic intensity. The prophylactic doses were studied for extended secondary VTE prevention in a population for whom there was clinical equipoise regarding continued anticoagulant therapy for VTE management.[29,30] Prophylactic doses have efficacy similar to that of treatment doses, and a recent meta-analysis of the apixaban and rivaroxaban trials described a trend toward less bleeding.[31] Protocolizing the definitions of provoked and unprovoked VTEs and high bleeding risk and defining for whom prophylactic doses are appropriate can improve the consistency of anticoagulant care delivery, and the AMS is uniquely positioned to facilitate these important elements of VTE management in systematic fashion.

Drug interactions

DOACs have fewer clinically relevant drug interactions than warfarin.[8] However, in the setting of significant P-gp or CYP drug interactions, there is no widely available test to assess the impact on coagulation status.[22] Similarly, the impact of DOAC drug interactions on bleeding and thromboembolism risk is often unclear. At a minimum, each patient considered for a DOAC must have drug interactions assessed before anticoagulant initiation. In addition, drug interactions should be reviewed with each renal function assessment. Integrated health care delivery systems can create alerts and administrative reports can be developed to notify the AMS of new critical drug interactions for patients receiving DOACs (and warfarin). Policies to avoid unnecessary antiplatelet therapy, nonsteriodal anti-inflammatory medications, and nonessential P-gp and CYP inducers/inhibitors should be available, including identification of which drug combinations must be avoided and/or require a switch to an alternative anticoagulant.

Invasive procedure planning

Interruption of anticoagulation for surgery and invasive diagnostic procedures poses increased risk for bleeding and thromboembolism.[32] Post hoc analyses of the DOAC AF trials found similar rates of bleeding and thromboembolism between warfarin and DOACs.[33-35] Bridge therapy with low molecular weight heparin is not needed during DOAC interruption because of their short half-lives and rapid onset after reinitiation.[8] The optimal timing of DOAC interruption and resumption around invasive procedures and high bleeding risk surgery to balance bleeding and thromboembolism risks has yet to be definitively determined, but guidance has been provided based upon the anticipated DOAC half-life and bleeding risk of the procedure.[8]

Effective communication between the proceduralist, patient, and anticoagulant prescriber (or the AMS) is critical to ensure all parties understand the bleeding and thromboembolic risks and the plan to minimize them during DOAC interruption. Unlike warfarin, for which a preoperative INR can confirm a patient has followed the recommended plan, there is no established test or guideline for parameters that represent a safe level for surgery for DOACs.[22] A normal thrombin time rules out meaningful dabigatran exposure, but mild elevation in a preoperative thrombin time may unnecessarily delay the procedure or increase use of idarucizumab.[22] Preoperative coagulation testing is not ready for routine use in patient care; therefore, communication and written instructions for patients are critical to ensure surgery or procedures can continue safely.

Adherence

Nonadherence to anticoagulant therapy is associated with increased hospitalizations and emergency department visits.[36-38] The Pharmacy Quality Alliance endorsed DOAC adherence as a potential quality measure for managed care plans in 2015.[36] More recently, the Centers for Medicare and Medicaid Services (CMS) proposed a measure for DOAC proportion of days covered of >80% as a potential 5-star measure for Medicare Managed Care and Part D plans.[39] Ultimately, CMS did not move forward with the DOAC adherence measure for 2019 requirements; however, health systems should be prepared for DOACs to join statins, oral diabetes agents, and angiotensin blocking agents as CMS adherence measures with reimbursement implications in the future.

Adherence to DOACs was high in the randomized controlled trials that supported their approval.[40] However, multiple analyses have described suboptimal adherence to DOACs in real-world data.[38,41] Early adherence in patients with AF is marginal, with proportions of days covered from 70% to 84%, but adherence seems to decrease even farther to 31.6% to 50.2% at 12 months.[38,41] These alarmingly low rates of adherence are a call to action, and the AMS is the optimal

resource to engage patients and drive adherence improvement interventions. An analysis of 67 Veterans Health Administration sites found that overall adherence to dabigatran was 74%. Adherence was greater at sites where pharmacy-led education and monitoring occurred, although the effect did not reach statistical significance after adjustment.[42]

Transitions between anticoagulants

Maintaining medication persistence is a challenge during anticoagulation, and drug therapy changes can occur at any time. Transitions from DOACs to warfarin are common, and having the AMS involved with both DOAC and warfarin management limits the fragmentation of anticoagulation care delivery.[38,41] Post hoc analysis of the ROCKET-AF trial, the randomized controlled trial comparing warfarin and rivaroxaban for stroke and systemic embolism prevention in AF, reported thromboembolic outcomes after study completion.[43] Fewer than 50% of patients transitioning from rivaroxaban to open-label warfarin achieved an INR >2.0 within 30 days of the transition.[43] In addition, patients transitioning from rivaroxaban to warfarin experienced significantly more strokes compared with patients continuing warfarin therapy. These transitions are clearly high-risk situations, and having an anticoagulation specialist assigned to a patient's longitudinal care is optimal to manage transitions as they are needed. In addition to effective warfarin dose selection, other issues to be addressed during transition back to warfarin include whether low molecular weight heparin bridging is needed, whether the DOAC will be overlapped with warfarin, and whether the DOAC interferes with the INR reading (and if so, how long after the last DOAC dose should the INR sample be drawn).

Conclusion

The full potential of the DOAC class of anticoagulants has yet to be realized. Reports of increasing anticoagulant ADEs in the United States suggest there remains a need for a robust, systematic approach to anticoagulant care delivery, whether patients are receiving DOACs or warfarin. Trained clinicians with specialized knowledge and expertise in anticoagulant therapy care delivery are currently available within the traditional AMS, and these are the logical resources to optimize DOAC drug therapy. Future research is needed comparing bleeding and thromboembolic outcomes in patients prescribed DOACs managed within an AMS vs managed with usual care. The absence of such data remains a barrier to widespread investment and integration of DOACs into traditional AMS structures.

Correspondence

Nathan P. Clark, 16601 East Centretch Parkway, Aurora, CO 80011; e-mail: nathan.clark@kp.org.

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