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ISMP Medication Safety Alert!®
Educating the Healthcare Community About Safe Medication Practices

Antithrombotic therapy—Advancing stewardship beyond anticoagulation—Part I

Problem: Despite years of progress in standardizing high-alert medication practices, organizations may find that traditional anticoagulation stewardship programs—primarily focusing on warfarin—often lack capacity to keep up with a rapidly expanding array of antithrombotic therapies. Antithrombotic therapies are medications that help prevent or treat harmful blood clots. They include antiplatelet drugs, which reduce the ability of platelets to clump together, and anticoagulant medications, which slow the body's clotting process. These medications work in different ways to lower the risk of heart attacks, strokes, and clot-related problems, while prescribers must work to carefully balance the risk of bleeding.[1] Anticoagulant medications continue to contribute disproportionately to serious adverse drug events in acute care settings and these risks frequently stem from the combined use of anticoagulants with antiplatelet agents and periprocedural medications.

The arrival of direct oral anticoagulants (DOACs) with their improved safety profiles, also brought much-needed simplicity to the prevention and management of thromboembolic events without the need for complex pharmacokinetic monitoring;[2] however, this simultaneously introduced a new set of complexities at the systems level. Each DOAC carries dose adjustments tied to patient age, indication, renal function, body weight, interacting agents, and procedural timing requirements. Errors such as inappropriate dosing, inconsistent periprocedural interruption strategies, and missed doses during transitions of care have been reported. These events reflect systemic gaps rather than a lack of practitioner knowledge; without a comprehensive review process, these high-alert therapies are difficult to manage reliably.

A broader antithrombotic perspective is required, given the multitude of limitations identified with a solely anticoagulant-focused approach. Just as stewardship efforts expanded from antibiotics to antimicrobials in the area of infectious disease, modern antithrombotic therapy demands a comprehensive and integrated approach. The scope of the problem is now bigger than just anticoagulants. Bleeding and blood clot risks often arise from using several medications together, including anticoagulants, antiplatelet drugs (e.g., aspirin, clopidogrel), medications used during procedures, "bridging" therapies, and reversal agents.

Practitioners in different departments make choices that affect a patient's overall risk. However, no single department typically has oversight of the whole picture. For example, simultaneously, a cardiologist may prescribe an anticoagulant to prevent stroke in a patient with atrial fibrillation in the ambulatory setting, an antiplatelet drug may be prescribed postoperatively by a cardiac surgeon after a heart procedure, and a hospitalist might want to prescribe medication for blood clot prevention prior to a future hospital admission. Without centralized oversight, aided by robust medication reconciliation processes during transitions of care, errors can occur.

Transitions of care, especially among departments and at hospital discharge, make the potential for harm from these medications particularly risky. Patients may be sent home with incorrect medication lists, continue taking medications they should only get in the hospital, or fail to restart their medications at the right time after procedures. One example reported to ISMP was from an institution that found frequent discontinuation of **ELIQUIS** (apixaban) after completion of the starter pack, where patients stopped the medication entirely. This often occurs when hospitalists

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Warning! Vancomycin labeled "DYE FREE" contains red dye. A pharmacist reported concerns about how vancomycin 250 mg/5 mL oral solution (NDC 69238-2261-03) by Amneal states "DYE FREE" on the bottle label (**Figure 1**); however, the prescribing information lists FD&C Red No. 40 ("red dye No. 40") as an inactive ingredient. The pharmacist had special ordered this formulation for a patient with a documented red dye allergy (anaphylaxis) due to the packaging stating "DYE FREE." Fortunately, the pharmacist double-checked the prescribing information prior to dispensing, so the patient was not harmed.

Figure 1. The label on Amneal's 250 mg/5 mL vancomycin oral solution states "DYE FREE," but FD&C Red No. 40 is listed as an inactive ingredient in the prescribing information.

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defer prescribing a continuation supply to outpatient providers, but the follow-up is incomplete or delayed, resulting in an unintended interruption of anticoagulation therapy. Many patients do not understand why they are taking these drugs or how long they need to take them. DOACs especially require robust follow-up, as routine blood tests are not used for monitoring. Changes in kidney function, interactions with other medications, and nonadherence can all cause serious harm if not monitored closely.

Real-World Antithrombotic Mishaps

These recent events reported to ISMP serve as a powerful reminder of the urgent need for stewardship transformation that encompasses antithrombotics in general.

*A patient admitted to the hospital was taking 10 mg of the DOAC **XARELTO** (rivaroxaban) daily for approximately two years after hip arthroplasty. This far exceeds the 3-week course that the prescriber intended for deep vein thrombosis (DVT) prophylaxis. Their primary care physician had been continuously renewing the prescription for approximately two years, admitting that a lack of communication since the initial discharge from the hospital led to a failure to recognize the drug's intended limited duration.*

*Following a percutaneous coronary intervention (PCI) procedure, a patient was inadvertently prescribed and dispensed **EFFIENT** (prasugrel) and **PLAVIX** (clopidogrel) due to a communication breakdown after a prescription change. Despite canceling the initial prasugrel prescription in the electronic health record (EHR), the prescriber failed to directly notify the community pharmacy. Due to a lack of system integration, the pharmacy dispensed both drugs to the patient. Consequently, the patient took both antiplatelet medications, along with aspirin and Eliquis for eight days before the error was identified.*

*A 95-year-old patient, admitted with a severe gastrointestinal (GI) bleed and an extremely elevated international normalized ratio (INR) of 19, was taking warfarin 5 mg twice daily after being transitioned from Eliquis. The lack of clear communication between the pharmacy, prescriber, and patient resulted in a life-threatening situation involving significant bleeding, leading to anemia and acute kidney injury from hypovolemic shock, requiring the administration of the reversal agent **KCENTRA** (prothrombin complex concentrate) and blood transfusions.*

These situations are analogous to the challenges faced with antibiotics before formal stewardship programs were established to manage their use. At the time, antibiotic-related harm was common due to inconsistent prescribing, a lack of oversight, and the absence of systems to manage the increasing complexity of the medications. Organizations eventually realized that optimizing antibiotic use required a multidisciplinary team approach, data monitoring, standardized protocols, and organization-wide collaboration. These efforts have reduced the overprescribing of broad-spectrum antibiotics that drive resistance and minimize risks such as *Clostridioides difficile (C. diff)* infections.[3] Applying a similar stewardship approach to antithrombotic medications is now a necessity for ALL healthcare organizations.

Professional groups, including the National Quality Forum (NQF) and the Anticoagulation Forum, increasingly advocate for "stewardship-style" oversight of antithrombotic medications.[4] Despite these recommendations, which ISMP supports, some healthcare organizations have yet to fully embrace these strategies. Without a coordinated, systematic program, organizations risk preventable harm, inconsistent practices, and overwhelming individual practitioners with the complexity of managing these medications.

Safe Practice Recommendations: Organizations should consider the following when building a comprehensive antithrombotic stewardship program.

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The pharmacist notified the manufacturer, who confirmed that this product contains red dye. According to DailyMed, there was a label update in April 2026, which no longer includes "DYE FREE." We reached out to the US Food and Drug Administration (FDA) and Amneal to report this concern. This is a potentially life-threatening situation for patients with an anaphylactic reaction to certain dyes. We have not heard back from Amneal whether organizations who have purchased this product have been or will be notified of this mislabeling, or if they plan to recall this product.

Medications are formulated with inactive ingredients for a variety of reasons such as enhancing stability, absorption, appearance (e.g., dyes), or taste, but certain ingredients can be a hidden source for allergen exposure. Manufacturers should explicitly identify a product's inactive ingredient content on the package and label, and in the prescribing information to help ensure this information is readily available. This is especially important for medications with an inactive ingredient known to be an allergen. Drug information, electronic health record (EHR), and pharmacy software vendors will then be able to take advantage of this information to provide enhanced clinical decision support.

Hospitals and pharmacies who purchase vancomycin 250 mg/5 mL oral solution (NDC 69238-2261-03) by Amneal must be aware that it contains red dye No. 40. If you purchased this as a "dye free" option, sequester it and consider alternative products. This good catch speaks to the importance of completing a comprehensive review of packaging and labeling when new drug products are purchased. To identify inactive ingredients in medications, review the package/label and prescribing information, and/or contact the manufacturer. Evaluate your EHR and pharmacy dispensing software to determine if an alert would be triggered if the patient had a documented allergy to an inactive ingredient. Incorporate inactive ingredients as part of the review process when evaluating new drugs or formulations and prior to purchasing. For additional information about inactive ingredients, refer to our April 24, 2025 article, Food-Drug Allergies—Inactive Ingredients Taking Active Roles.

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Establish an antithrombotic stewardship program. If not already in place, develop an antithrombotic stewardship program that provides oversight to achieve optimal outcomes and minimize medication errors. A successful program starts with an interdisciplinary team, which may include pharmacists, hematologists, cardiologists, hospitalists, intensive care providers, nursing leaders, quality and safety experts, laboratory, and information technology (IT) representatives. This team should be empowered to create protocols and order sets, oversee medication choices, coordinate periprocedural medication management, review complex cases, measure program performance, and lead improvement projects.[4]

Develop standard protocols. Standardized protocols should include dosing for anticoagulants based on indication and recommendations for dose adjustments based on patient-specific factors. Protocols should also differentiate anticoagulant use for prophylaxis versus treatment. Antiplatelet protocols should outline the duration of dual or triple therapy after procedures and identify when to stop medications to reduce bleeding risk. Protocols should include guidance for bridging antithrombotic therapy during the perioperative or postprocedural period in both inpatient and outpatient settings.[4]

Create comprehensive order sets. Use disease-specific guidelines to build antithrombotic order sets in the EHR that guide prescribers to select the appropriate dose, frequency, and duration based on indication and patient-specific factors outlined in the protocols. Incorporate baseline laboratory test requirements and monitoring parameters for efficacy and safety. Include reversal agents in order sets with directions for use and administration.

Leverage clinical decision support. Use clinical decision support for dose range checking and laboratory triggers. This is critical in ensuring that practitioners are alerted to drug-drug and drug-disease state interactions (e.g., hard stop based on renal function).

Self-assess. As part of a comprehensive approach, organizations should use the ISMP Medication Safety Self Assessment® for Antithrombotic Therapy to evaluate current practices and identify areas for improvement in safe antithrombotic use. This self-assessment tool provides a framework for organizations to enhance safety and track progress over time.

Monitor data in real-time. Organizations should use data systems to proactively identify risk, in addition to reviewing data retrospectively after an error occurs. Automated tools can flag inappropriate antithrombotic doses, duplicate therapies, declining renal function and other laboratory results, missing indications, prolonged medication use, or dangerous drug interactions. Pharmacists or team members can review these alerts and intervene. Dashboards that track bleeding and thrombotic events, dosing accuracy, and protocol adherence can support monitoring and allow for rapid corrections. This is similar to how antibiotic stewardship evolved from manual reviews to leveraging automated data.[4]

Improve transitions of care. Effective transitions depend on accurate medication lists, clear communication, and patient education. Stewardship teams should have a process where a specialized practitioner with advanced training, often a pharmacist, verifies the indication, dose, duration of therapy, and its appropriateness before initiating therapy and before the patient is discharged. Discharge instructions must address missed doses, signs of bleeding or clots, timing for procedures, and who to contact with questions. Hospitals should ensure that discharge summaries have clear fields for the medication indication and duration of use, and that outpatient providers receive timely notifications about needed laboratory tests or follow-up care. Automated reminders for renal function monitoring or adherence checks can support safety after discharge.[4]

Promote safe deprescribing. Stewardship must include strategies to prevent therapy from continuing longer than necessary, as this is a cause of preventable bleeding. Stewardship teams should have a process to reassess the duration of therapy after procedures, provoked venous thromboembolism (VTE), atrial fibrillation episodes during illness, or when therapy was started in the hospital without a clear long-term reason. Practitioners should regularly evaluate if there is a continued need for aspirin in patients already receiving anticoagulants to reduce the risk of bleeding.

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HIGH-ALERT

Ketamine overdose following ADC override without BCMA. A prescriber ordered 1 mg/kg of ketamine intravenously (IV) for a 73 kg trauma patient during a code in the ED. The prescriber entered the medication order into the electronic health record (EHR), which the pharmacist was in the process of verifying, and simultaneously provided a verbal order to the nurse. The nurse, who was a new practitioner and new to the organization, intended to remove a 200 mg/20 mL (10 mg/mL) vial and prepare a 73 mg/7.3 mL dose. However, when the nurse searched for ketamine in the automated dispensing cabinet (ADC), she selected the first entry, the 500 mg/5 mL (100 mg/mL) ketamine product. In this organization, this product is for intramuscular (IM) and intranasal use only. To provide a volume of 7.3 mL, she removed two vials via override and prepared a dose of 730 mg (instead of 73 mg). The nurse administered the dose, bypassing barcode medication administration (BCMA). After administration, she went to document in the medication administration record (MAR), identified the error, and notified the prescriber. No harm was reported, as the patient was already intubated.

The organization has since limited access to the 100 mg/mL ketamine concentration to only one ADC outside of the main ED area. They have also added an ADC alert upon selection of the 100 mg/mL product, warning that this is for IM and intranasal use only.

Organizations should evaluate which drugs (including different concentrations of the same medication) are available in each ADC location. Limit the variety of medications that can be removed from an ADC using the override function. Develop order sets (e.g., trauma-specific) and require prescribers to enter medication orders in the EHR to maximize the benefit of clinical decision support and proactive pharmacist review. Use BCMA prior to administration, including in the ED. During code situations, label all practitioner-prepared infusions and syringes, and read labels aloud prior to administration. When possible, have a second code team member independently check the dose and volume prior to administration and also share the source vial so that the drug and dose can be confirmed during the double check.

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Share decisions with patients. Decisions about antithrombotic therapy often involve balancing thrombotic and bleeding risks, making shared decision-making essential. Stewardship programs should empower practitioners by providing tools for discussing stroke prevention in atrial fibrillation, the risks and benefits of combination therapy, and realistic expectations about bleeding risk. Teams should also support deprescribing conversations for patients with high fall risk or difficulty adhering to complex regimens.

Educate practitioners. Practitioner education should be continuous and tailored to distinct roles. Educational materials should be easy to understand for all patients, and practitioners should ensure patients understand why they are receiving the medication, how long they should take it, and what symptoms need urgent evaluation. Organizations should implement initial and annual competency assessments for prescribers, nurses, and pharmacists. Ensure practitioners can recognize patient symptoms or changes in their condition that may require intervention or a change in therapy. Interdisciplinary collaboration between specialists, including hematology, cardiology, neurology, emergency medicine, and surgery, helps ensure alignment across disciplines. Regularly reviewing cases, adverse events, and performance trends to share lessons learned can support a culture of safety and reinforce risk recognition and mitigation.

Coach patients. Equally important, patients should be educated about their antithrombotic dose, signs of toxicity, and what to do if they miss a dose. During the medication reconciliation process, practitioners should ask scripted questions and specifically ask about prescription and over-the-counter (i.e., aspirin) antithrombotic use. During discharge counseling, confirm there is a plan for the patient's outpatient follow-up appointments (e.g., primary care physician, hematologist, anticoagulation clinic). Share educational resources such as the Medication Safety Tips: High-Alert Medicines for certain anticoagulants on the ISMP consumer website.

Conduct quality reviews. Continuous improvement requires ongoing evaluation. Stewardship teams should conduct reviews of high-risk cases, bleeding and thrombotic events, and missed opportunities for deprescribing or dose adjustment. Root cause analyses can identify system weaknesses like workflow gaps, unclear documentation, or ineffective decision support tools. Organizations should report performance metrics to quality committees, service line leaders, and frontline practitioners, recognizing departments that show improvement and address persistent challenges.

Conclusion

ISMP recognizes the value of antithrombotic stewardship programs to reduce the risk of harm associated with these medications. However, the often complex and time- and labor-intensive nature of these programs may have been a barrier to enhancing care in some organizations. We plan to publish a follow-up article, **Part II**, describing how an organization was able to optimize its program through the expansion of clinical decision support to guide practitioners.

Contributing author Kara Jensen, PharmD, BCPS; 2025-2026 ISMP Safe Medication Management Fellow, supported by the US Army

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Unlabeled bottles found inside methadone-labeled cartons. Two pharmacies have received cartons of methadone oral concentrate 10 mg/mL (NDC: 00527-1927-36, lot number 25283060B), by Lannett, containing bottles without affixed labels (**Figure 1**). It is unclear if this problem is isolated to the indicated lot. However, one reporting pharmacy shared that they had the same product from a different lot that contained a properly labeled bottle.

Figure 1. A carton of methadone oral concentrate (10 mg/mL) from Lannett. The outer carton lists the drug information; however, the inside bottle is unlabeled.

ISMP has notified the manufacturer and the US Food and Drug Administration (FDA). We urge organizations to inspect your stock of Lannett methadone oral concentrate. If you discover any cartons containing unlabeled bottles, immediately sequester the affected product. Contact Lannett for guidance and report the issue to FDA and ISMP.

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