

Pa Patient Saf Advis 2018 Jun;15(2).

Identifying Patient Harm from Direct Oral Anticoagulants

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* The views expressed in this article are those of the author and do not reflect the official policy or position of the U.S. Air Force, U.S. Department of Defense, or the U.S. Government.

Abstract

Direct oral anticoagulants (DOACs), a newer class of oral anticoagulants, have been promoted as a safer and more effective option than warfarin. A query of the Pennsylvania Patient Safety Reporting System (PA-PSRS) database for events involving DOACs that occurred from January 2011 through August 2017 revealed 1,811 reported events, including 265 that resulted in patient harm. The data from these reports were categorized into two groups: harmful events (i.e., adverse drug events) (14.6%, n = 265) and medication errors without harm (85.4%, n = 1,546). Hemorrhage was the most frequently reported adverse event (70.2%, n = 186 of 265). Almost 40% (38.5%, n = 102 of 265) of harmful events occurred to patients who were 80 years or older. Duplicate therapy (33.3%, n = 515 of 1,546) was the most frequently reported type of error without harm. Employing standard protocols to guide therapy, reviewing baseline patient information, including patient weight (in metric units) and laboratory test results such as renal and liver function, and considering the therapeutic indication can aid selection of an appropriate anticoagulant medication for patients.

Introduction

About 2.6 million people have atrial fibrillation in the United States, and that number is expected to rise to 12 million by the year 2050.¹ Anticoagulants are routinely used in these patients to help prevent and treat thromboemboli related to this arrhythmia.²⁻⁵ Direct oral anticoagulants (DOACs)—including apixaban (Eliquis®), dabigatran (Pradaxa®), edoxaban (Savaysa™), and rivaroxaban (Xarelto®)—have grown to a combined 42% share of the U.S. oral anticoagulation market since the release of dabigatran in late 2010. In 2015, rivaroxaban was the most widely prescribed DOAC, accounting for 29% of all ambulatory anticoagulant orders.¹

Additionally, apixaban, dabigatran, and rivaroxaban have gained approval for postoperative deep vein thrombosis (DVT) prophylaxis for knee and hip replacements, indications for which warfarin (Coumadin®) had previously been the primary medication of choice.⁶ Before the development of the first DOAC, dabigatran, warfarin had been the primary oral anticoagulant and heparin was the most used injectable anticoagulant.

Warfarin pharmacokinetics make achieving desired effects complicated because it has a highly variable rate of elimination, slow onset of action, and a long half-life. Warfarin works as a vitamin K antagonist, interacting within many different points along the coagulation pathway, specifically affecting factors II, VII, IX, and X. These issues with warfarin increase the difficulty of ensuring the patient has a safe and therapeutic dose. Even at therapeutic doses, all anticoagulants have the risk of causing a spontaneous hemorrhage, and even mild trauma can lead to severe complications from a resulting hemorrhage.

Effective and safe use of warfarin also requires detailed patient assessment, regular monitoring, and the potential for frequent, patient-specific dose adjustments to minimize the high risk of hemorrhage. It has been estimated that a patient on warfarin has a 15% to 20% annual risk of developing a hemorrhage and a 1% to 3% chance of having a severe hemorrhage.⁷ Additionally, warfarin has a large number of drug-drug interactions along with varied efficacy related to the patient's dietary intake of foods rich in vitamin K. One study shows that even adherent patients whose warfarin dosage is stable are within their therapeutic range only about 55% of the time.⁸

It is not surprising that a new class of oral medications was seen as a leap forward for anticoagulant therapy. DOACs have a fixed, indication-based dosing; short half-life; and quick onset of action. Additionally, as the drug-class name implies, they work "directly" on a single pathway, inhibiting either factor Xa (apixaban, betrixaban [Bevyxxa®], edoxaban, rivaroxaban) or thrombin (dabigatran). Although enoxaparin (Lovenox®) and fondaparinux (Arixtra®) also selectively inhibit factor Xa, they are available only in injectable formulations, which is not preferred for long-term outpatient treatment.

Data from both the U.S. Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) shows that oral anticoagulants continue to be one of the leading causes of hemorrhages and account for about 17.6% of all emergency department (ED) visits.^{9,10}

Pennsylvania Patient Safety Authority analysts reviewed errors associated with the use of DOACs distinct from warfarin. Analysts sought to characterize the types of events that occurred with these medications, identify contributing factors, and describe system-based risk reduction strategies.

Methods

Analysts queried the Pennsylvania Patient Safety Reporting System (PA-PSRS) database for events related specifically to DOACs that occurred from January 2011 through August 2017. Portions of each DOAC's proprietary and nonproprietary name, to account for possible misspellings, were used to search applicable drug name and event

description fields. The query resulted in 2,610 reports. Of these, 799 reports were excluded for lack of relevance, most frequently because the anticoagulant mentioned within the report did not contribute to the event (e.g., a DOAC was prescribed after an event occurred). The final detailed analysis yielded 1,811 event reports.

Analysts categorized the events using a number of criteria, including whether or not the event resulted in patient harm. Questions used by analysts to categorize events included:

- Did the patient require medical intervention or was medical treatment sought or required?
 - Did the event result in harm to the patient?
 - What type of harm occurred to the patient?
 - Did the report specify that the patient had a hemorrhage?
 - In what area of the body did the hemorrhage occur?
- Was the adverse event due to a medication error?
- Was an antidote or blood product given to mitigate the adverse effect of a DOAC?
- Was the DOAC treatment regimen changed (e.g., to a different anticoagulant)?
- Did the use of a DOAC result in procedure cancellations or complications?
- Did a patient require a transfer to a higher level of care or an extended hospitalization?

Reports that were determined to involve harm were labeled as adverse drug events (ADEs) and required the report to specifically mention that a patient experienced an untoward effect from a DOAC (e.g., hemorrhage). ADEs can include events that are considered preventable (i.e., medication errors) or unpreventable (i.e., adverse drug reactions). DOAC errors without harm, for this portion of the analysis, consist of preventable events that could have or did result in an error but did not cause harm to the patient.

Events were considered to involve "improper bridging" when a DOAC was intentionally used concomitantly with warfarin until the therapeutic international normalized ratio (INR) goal was reached. These reports are excluded from the event type therapeutic duplication because the report details were specific enough for analysts to determine that the duplication was intentionally chosen as a bridging treatment.

Reports were also analyzed based on the patient age, medication name, event type, event description, and nodes of the medication use process as provided by the reporting facility. Analysts completed the medication-name field in reports in which a medication-name data field was left blank or incomplete but the name was provided in the event description.

Results

Of the 1,811 reports, 14.6% (n = 265) were considered ADEs and 85.4% (n = 1,546) were medication errors without harm. Three DOACs were identified in the submitted reports (Table). There were no reports involving edoxaban or betrixaban. As use of DOACs in clinical practice has increased, so too has the number of reports involving these agents submitted to the Authority (Figure 1).

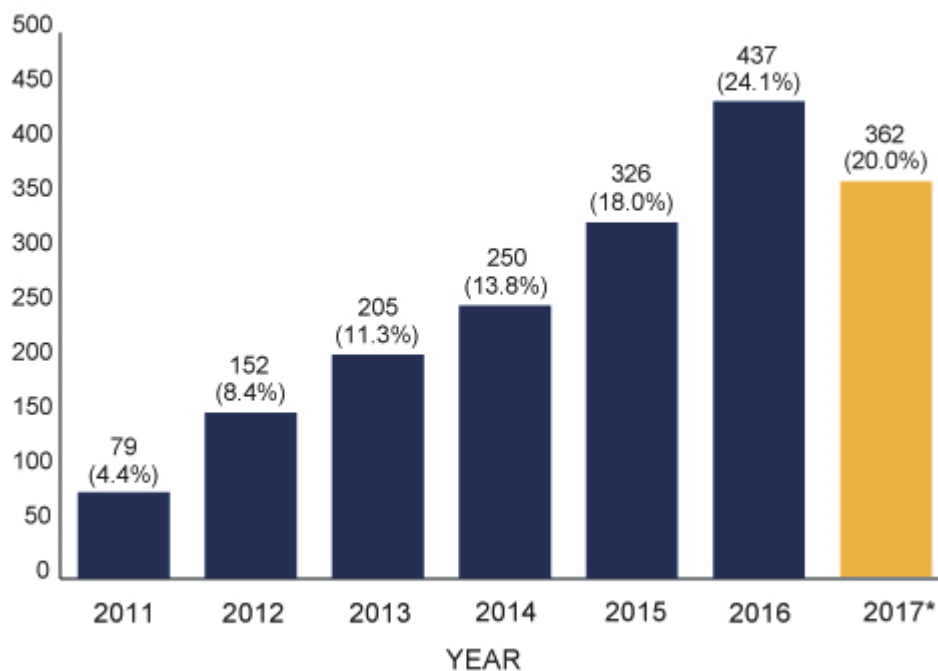
Table. Direct Oral Anticoagulants Involved in Reported Events (N = 1,811)

Drug	No. (%)
Rivaroxaban	922 (50.9)
Apixaban	544 (30.0)
Dabigatran	345 (19.1)

Note: Data reported through the Pennsylvania Patient Safety Reporting System, January 2011 through August 2017.

Figure 1. Number of Events Involving Direct Oral Anticoagulants, by Event Year (N = 1,811)

NUMBER OF REPORTS



* Represents only a partial year (January 2017 through August 2017).

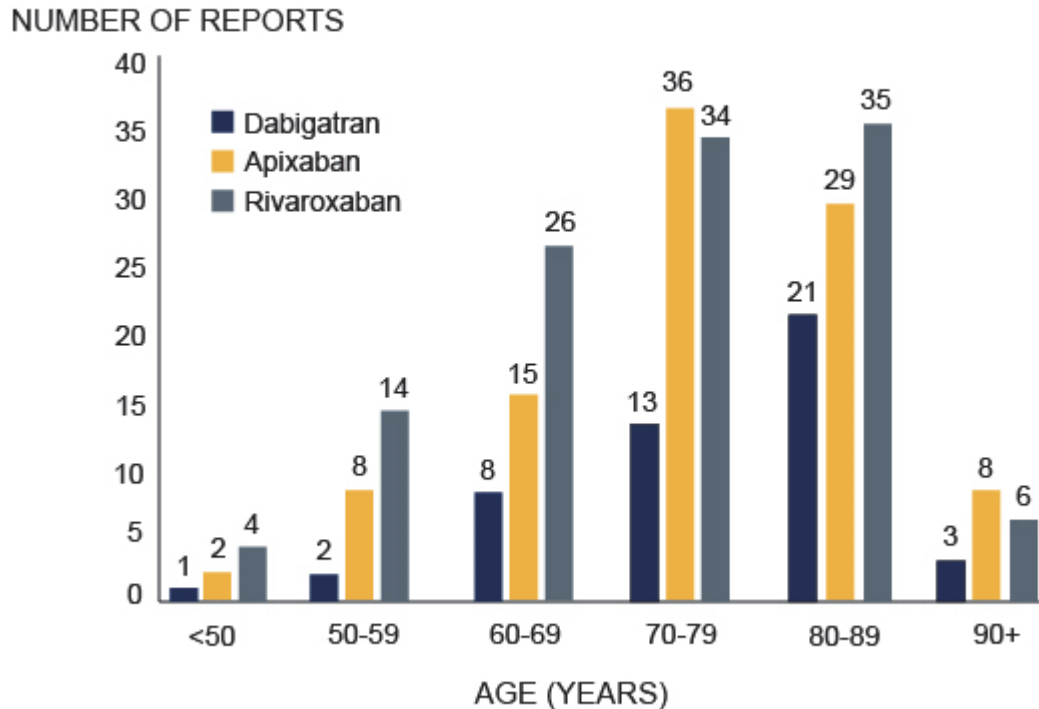
Note: Data reported through the Pennsylvania Patient Safety Reporting System, January 2011 through August 2017.

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Adverse Drug Events

The average age of a patient who experienced harm was 74.5 years. Breakdown by decade of life shows an increase in the number of adverse events over each decade of life until the over-90 group (Figure 2). Analysis of adverse events by gender shows that 135 of 265 events (50.9%) involved females compared with 130 (49.1%) males.

Figure 2. Number of Adverse Drug Events Involving Direct Oral Anticoagulants, by Decade of Patient Age (N = 265)



Note: Data reported through the Pennsylvania Patient Safety Reporting System, January 2011 through August 2017.

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Analysts identified that 14.6% (n = 265 of 1,811) of the events described some type of patient harm. This included 2 reports of patient death, 10 reports of embolic stroke, 5 reports of hemorrhagic stroke, and 1 case of Stevens-Johnson syndrome. The two deaths reported were due to hemorrhages—one gastrointestinal (GI) and the other pulmonary. Both reports resulting in a death also stated that the patients had received a non-DOAC anticoagulant before switching to rivaroxaban. The reported data was insufficient to determine whether improper selection or management of anticoagulation medications contributed to the deaths. Following are the two reports of patient death:*

The patient had an RRT [rapid response team] [call]. [Two days later] a mid-line was placed and the patient was noted to have post-procedure bleeding. The patient received 2 units of packed red blood cells. The patient was receiving enoxaparin [for five days] [followed by] rivaroxaban on [the day of the mid-line insertion]. The patient coded and was found to have a massive GI bleed. The patient, despite reversal of [the anticoagulants] and having his intravascular volume repleted, expired the next night.

Patient was taken off Coumadin [warfarin] and placed on Xarelto [rivaroxaban]. The patient developed a hematoma secondary to Xarelto most likely, and this showed up on CT [computerized tomography] scan of the chest and CT scan of the thorax—large left retroperitoneal bleed. Shortly after he was transferred to ICU [intensive care unit], he went into respiratory failure. Shortly after, the patient expired.

The most common type of outcome reported was hemorrhage, at 84.2% (n = 223 of 265). The remaining types were allergic reaction 4.5% (n = 12), embolism 3.8% (n = 10), abnormal lab value 3.4% (n = 9), gastritis 1.9% (n = 5), and other 2.3% (n = 6). Rivaroxaban was associated with the largest percentage of ADEs (44.9%, n = 119), followed by apixaban (37.0%, n = 98) and dabigatran (18.1%, n = 48).

Analysts found that 88.3% (n = 234 of 265) of reports noted that patients required medical treatment when an adverse event occurred. One-third (33.8%, n = 234) of the events requiring medical treatment resulted in administration of an antidote or blood transfusion to treat the hemorrhage.

Prescribers in 31.7% (n = 84 of 265) of ADEs discontinued the suspect drug and initiated a new treatment plan. The patient's DOAC dose was either held or reduced in 16.2% (n = 43) of adverse events. Analysts were unable to determine the status of the medication order in 46.8% (n = 124) of the adverse event reports.

* The details of the PA-PSRS event narratives in this article have been modified to preserve confidentiality.

Anatomic Site of Hemorrhage

More than three-quarters of the reports involving hemorrhage (83.4%, n = 186 of 223) identified the site where bleeding occurred. GI tract was the most common hemorrhage location (48.9%, n = 91 of 186). Upper GI tract (31.2%, n = 58) was more commonly reported than lower GI tract (17.7%, n = 33). Other anatomic hemorrhage sites included urinary (12.4%, n = 23), surgical (10.8%, n = 20), cerebral (8.6%, n = 16), nasal (5.9%, n = 11), multiple sites (2.7%, n = 5), and other (10.8%, n = 20). Additionally, 11 reports noted a required transfer of the patient to a higher level of care within the hospital or to a different facility. Following is an example of event resulting in a hemorrhage, reported through PA-PSRS:

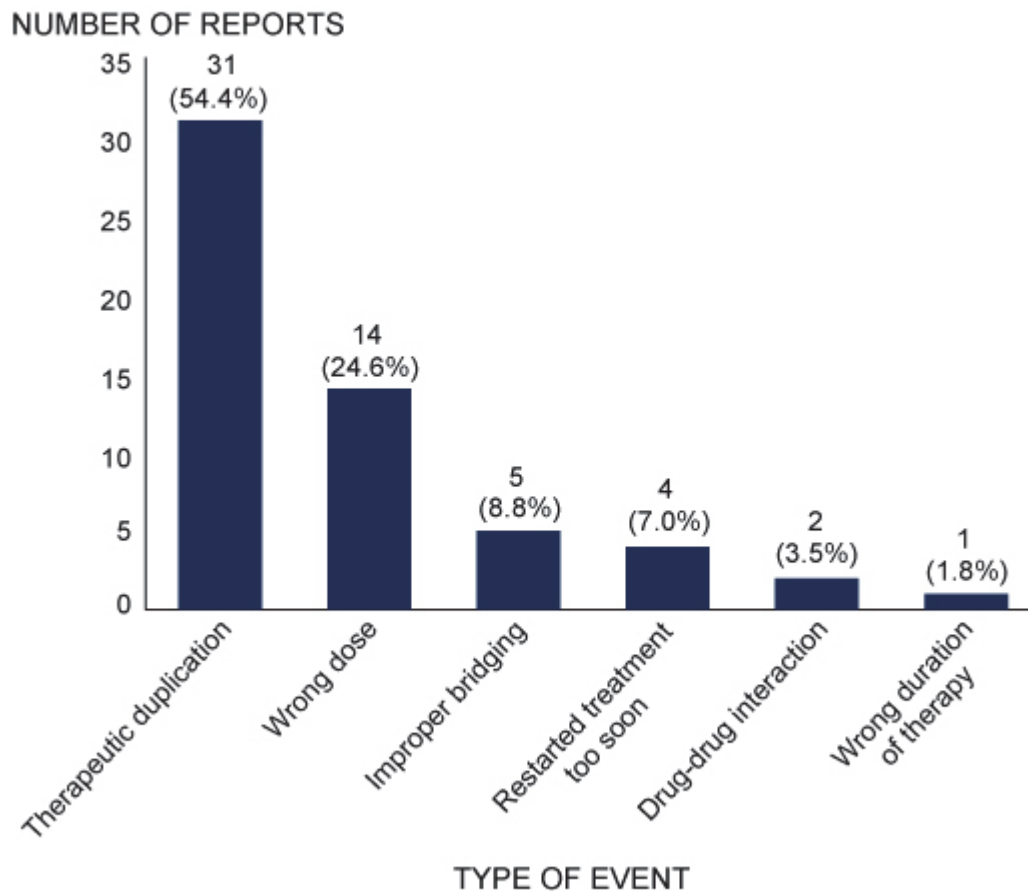
A 63 y/o female patient was admitted pre-op on Plavix® [clopidogrel] and Coumadin. After the patient's right hip arthroplasty, the patient was prescribed CeleBREX® [celecoxib], Xarelto, Coumadin, and Plavix. The patient took the medications [for four days]. GI [team] was consulted on [the second post-operative day] due to anemia and hematemesis. GI [team] said that her anemia was likely multifactorial and possibly due to taking multiple anticoagulants together.

Preventable Adverse Drug Events

Preventable errors were identified in 21.5% of the event reports involving harm (n = 57 of 265) (Figure 3). Analysts categorized these events into six types of errors: therapeutic duplication, wrong dose, improper bridging, restarted anticoagulation treatment too soon, drug-drug interaction, and wrong duration of therapy. Therapeutic duplication (54.4%, n = 31 of 57) and wrong dose (24.6%, n = 14) were the most common types of errors. Following are examples of preventable adverse drug events reported through PA-PSRS:

A 78-year-old patient had hip surgery in the fall and has not been as mobile since. She has recently started ambulating. She presented to the ED [emergency department] with left lower extremity swelling and pain. She was diagnosed with a DVT. The ED physician wrote for Lovenox [enoxaparin] 130 mg subcutaneously and decided to admit the patient to the hospital. The inpatient physician came to see the patient and prescribed Xarelto 15 mg 2 hours after the Lovenox was administered. The patient had a significant gastrointestinal bleed 24 hours after the duplicate therapy was administered. The patient went into shock and was transferred to the ICU. The patient was given factor IX, fresh frozen plasma, and packed red blood cells.

Figure 3. Types of Preventable Adverse Drug Events Involving Direct Oral Anticoagulants (N = 57)



Note: Data reported through the Pennsylvania Patient Safety Reporting System, January 2011 through August 2017.

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Patients who were improperly bridged accounted for 8.8% (n = 5 of 57) of the reports involving preventable errors. These five patients had an average age of 86.8 years, with one requiring a transfer to the ICU. Following are examples of inappropriate bridging events reported through PA-PSRS:

87 y/o male patient received warfarin. Dabigatran was started as a "bridge to Coumadin therapy." Patient transferred to ICU. Patient developed bilateral nasal bleeding. Received vitamin K, fresh frozen plasma, and packed RBCs. The aPTT [activated partial thromboplastin time] result was elevated.

92 y/o female patient admitted with hydropneumothorax. Had been taking apixaban 2.5 mg bid [twice a day] at home, and this was resumed [on the fourth day of the admission]. [Four days later] she was also started on warfarin 5 mg with plan to continue apixaban x 3 doses as bridge. [The next day the patient] was noted to have hematuria, INR = 1.6. Apixaban was discontinued and warfarin was continued. INR [the next day] was 1.7 with no additional bleeding documented.

89 y/o female patient was discharged in October after admission for atrial fibrillation. She had been on a cardiac heparin protocol during admission and PTT [partial thromboplastin time] was 45 in the morning prior to discharge. She was [started on] warfarin [a day] prior to discharge. No INR was drawn. Discharge instruction for this admission listed warfarin 4 mg daily. Patient was given Pradaxa [dabigatran] 150 mg prior to discharge with samples of Pradaxa to take home. The Pradaxa was not listed on the discharge instructions. Patient was admitted again to critical care for lower GI bleeding. Admissions paperwork noted patient being bridged with Pradaxa. INR on admission was 2.27 and vitamin k 2 mg was given IV. Hemoglobin was 11.0 prior to discharge and was 9.3 when readmitted.

DOAC Errors without Harm

DOAC errors without harm were categorized into nine specific types of events. The three most common types of events accounted for 66.6% (n = 1,030 of 1,546) of all errors without harm (Figure 4). These three categories were therapeutic duplication, dose omission, and wrong dose. As Figure 5 shows, the medications most commonly involved in DOAC duplicate therapy events without harm were heparin (56.1%, n = 289 of 515); enoxaparin (29.9%, n = 154), and warfarin (8.0%, n = 41). Of the 289 instances when heparin was given, 101 reports were identified as heparin infusions. Following are examples of errors without harm reported through PA-PSRS:

53 y/o male patient in OR [operating room] for hip replacement, on Eliquis [apixaban] at home - this was entered to continue home therapy here. Then the orthopedic resident entered an order for rivaroxaban. One problem - physician did not recognize duplicate drugs, two - computer does not screen for duplicates when item is entered as non-formulary.

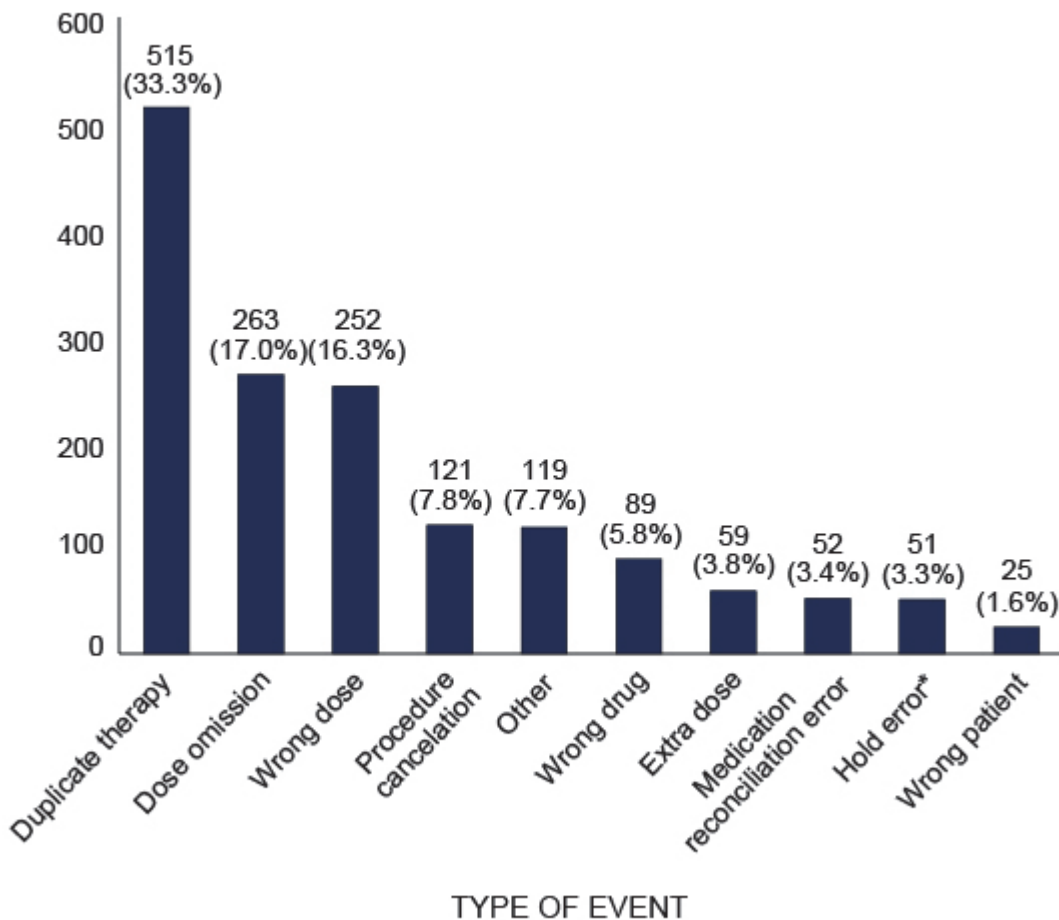
Pharmacist reported 67 y/o female post-TEE [transesophageal echocardiography] orders written to discontinue Coumadin & start Eliquis when INR less than 2. Coumadin regimen not removed from profile. Error noted two days later when order for Coumadin received. Pharmacist called MD to clarify med orders. New orders to discontinue Coumadin & start Eliquis.

93 y/o male had orders written for digoxin and Xarelto, doses missed, never entered into medication administration system. IV ordered was entered into system but was not started. Med errors found upon review of chart orders.

According to medication reconciliation history, it was documented that patient was taking rivaroxaban 20 mg bid for DVT. For patient with good renal function, it is dosed 15 mg bid for 21 days and then 20 mg daily. Pharmacist verified the dose and patient received 20 mg on [two consecutive days]. Patient told us during rounds that he was taking rivaroxaban starter pack (15 mg bid for 21 days and 20 mg daily). Pharmacist should have identified the medication reconciliation error. Patient was not harmed.

Figure 4. Types of Preventable Events without Harm Involving Direct Oral Anticoagulants (N = 1,546)

NUMBER OF REPORTS



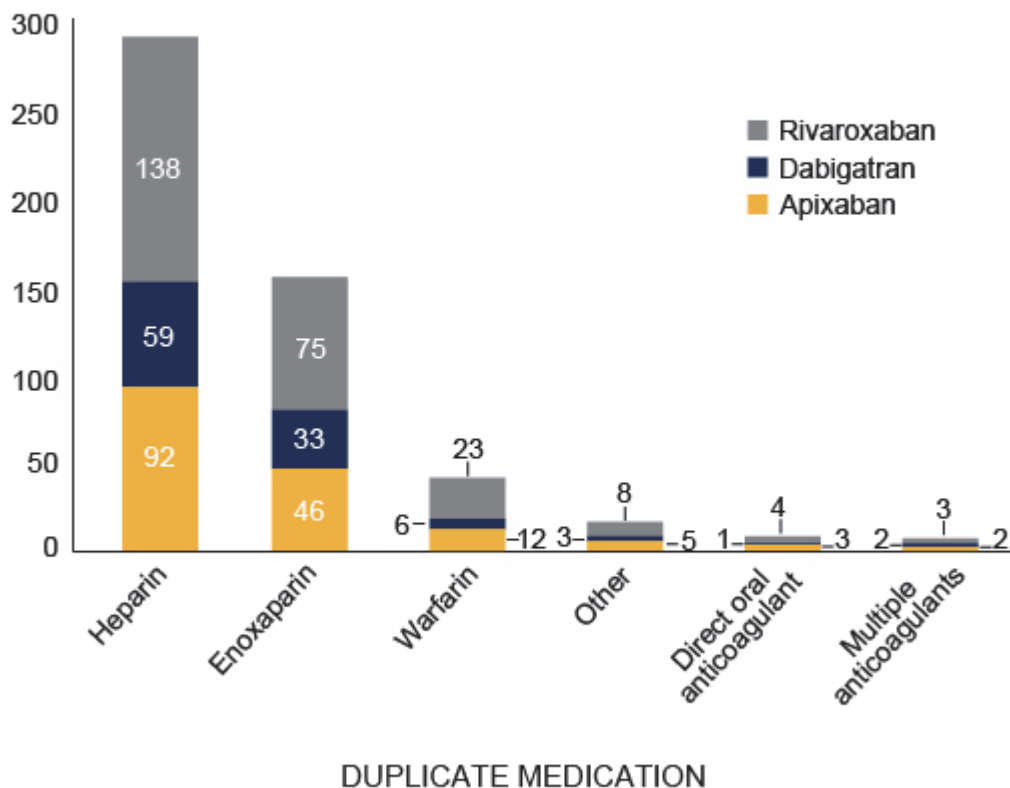
* Includes events in which the medication was held for too long, not held long enough, or not held.

Note: Data reported through the Pennsylvania Patient Safety Reporting System, January 2011 through August 2017.

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Figure 5. Anticoagulant Medication Pairs Involved in Therapeutic Duplication Errors without Harm (N = 515)

NUMBER OF REPORTS



Note: Data reported through the Pennsylvania Patient Safety Reporting System, January 2011 through August 2017.

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Procedure Cancellations and Complications

Outpatient procedure cancellations and complications due to patients either holding or not holding their DOAC were noted in 7.6% (n = 137 of 1,811) of reports. In 88.3% (n = 121 of 137) of those reports, the procedure was canceled when the DOAC had not been held. These events were caught by facility staff when conducting medication reviews during a pre-operative assessment.

Reports show that patient harm occurred in 16 events. Stroke or stroke-like symptoms were noted in 75.0% (n = 12 of 16) of the reports when the medication was held prior to the procedure. Two reports indicated stroke-like symptoms were identified prior to the patients' procedures. The remaining 10 patients were identified with stroke-like symptoms or with having an embolic event after their procedure. Clinician documentation of the error reports suggested that holding the patient's anticoagulant medication contributed to development of a postoperative embolic stroke or a DVT/PE (pulmonary embolism). One-quarter (25%, n = 4) of events resulted in patients developing a postoperative hemorrhage from not holding their anticoagulant medication. Following are examples of procedure cancellations or complications reported through PA-PSRS:

70 y/o female on postoperative day 2 was identified to have a possible CVA [cerebrovascular accident] due to impaired speech, expressive aphasia, and facial droop. Patient was transferred to [a different facility]. The patient had a CT scan, which revealed a double clot. IR [interventional radiology] initiated the procedure for mechanical thrombectomy. The patient spontaneously opened one occlusion. Physician regarded the event most likely cardioembolic, secondary to being off her Eliquis for her atrial fibrillation for the procedure. Pt made a full recovery.

81 y/o male 2 day post nephrolithotomy procedure unable to resume Xarelto because of bleeding, developed slurred speech and left-sided weakness. CT of the brain showed stroke and patient was transferred to tertiary care facility.

Patient underwent an UGI [upper gastrointestinal endoscopy] and colonoscopy for a history of abdominal pain, diarrhea, and weight loss. She was on Pradaxa for atrial fibrillation, which was stopped prior to the procedure. In the recovery area, she suddenly developed aphasia and confusion. A CT showed a stroke. She was admitted to the hospital.

Discussion

Therapeutic duplication was involved in more than half of preventable DOAC events associated with patient harm. Using two antithrombotic medications at the same time can increase the risk of patient harm even after administration of only a few doses. Heparin was involved in more than half of all therapeutic duplications. The high number of DOAC and heparin events could be influenced by limited understanding from prescribers and other healthcare professionals on how to prescribe, monitor, administer, and convert to or from these newer anticoagulants. Decision support systems should be designed properly to catch therapeutic duplication errors.

DOAC usage has increased every year since their release.¹ One reason is the benefit of not requiring INR-based dosing. Another is that DOACs have fewer drug-food and drug-drug interactions than warfarin.^{6,11,12} However, clinicians prescribing DOACs must still see the patient regularly. Instead of reviewing the INR results for warfarin dose titration changes to keep a patient safely anticoagulated, as is done with warfarin therapy, clinicians need to conduct a clinical review and ensure laboratory monitoring is up to date to ensure liver and kidney functions have not changed. Especially within the geriatric population, these steps are vital to ensure the DOAC is still the appropriate anticoagulant and the dose does not require adjustment for a patient's change in status.

The patient's age appeared to be a predominant risk factor within these reports. As patients age, they become more susceptible to harm when medication errors occur. Unfortunately, there is not strong clinical data to guide DOAC dosing in patients older than 75 years of age. Most of the pivotal DOAC clinical trials excluded patients who were older than 74 years.¹³ Reports submitted to the Authority showed that 38.6% of patient harm occurred in patients 80 years of age or older.

CDC estimates that the U.S. population has about a 2% chance of developing atrial fibrillation before the age of 65, and this risk increases to about 9% after age 65.^{9,14} Additionally, the risk of thrombosis (DVT or PE) for someone under 45 is 1:10,000, which gradually increases with each decade of life to about 6:1,000 by the age of 80.^{7,15} Currently, apixaban is the only DOAC with specific dosing recommendations for the geriatric population.²

Because DOACs are used to treat diseases that impact adult and elderly patients, prescribers should be cognizant of the patient's age along with any additional comorbidities that can increase the risk of a hemorrhage. Patients 80 or older have the highest risk of a major hemorrhage within the first 90 days of starting a DOAC, so it is highly recommended that additional clinical reviews and laboratory monitoring is completed during the first 90 days of therapy.^{12,16} All the trials used for DOAC approvals excluded patients with a creatinine clearance (CrCl) less than 25–30 mL/min for VTE studies or a CrCl less than 30 mL/min for nonvalvular atrial fibrillation (NVAF) studies.¹⁶

Use of dabigatran, especially, can be challenging because its renal dosing was never studied and, as a prodrug, it requires proper liver function for conversion to its active metabolite and proper renal function for elimination. Apixaban and edoxaban have been shown to be safer for the elderly population, but if kidney function is enhanced (CrCl greater than 95 mL/min) there is a risk of decreased edoxaban efficacy.¹⁷ It is important that an evaluation of the patient's liver and renal function be conducted before and during treatment to assess which DOAC is best for a patient.

Limitations

In-depth analysis by the Authority of events involving DOACs is limited by the information reported by facilities through PA-PSRS, including the event descriptions. As with all reporting systems, the type and number of reports collected depend on the degree to which facility reporting is accurate and complete. The reporting cultures and patterns in each facility, and their interpretations of what occurrences are reportable, can lead to reporting variations. Although the narrative fields of the reports help analysts discern what happened during the event, they often do not contain details describing how the event deviated from the standard operation or which factors contributed to the event.

The changing availability of the various DOACs over time limits the ability to make direct comparisons between DOACs or to determine whether one DOAC appears to be safer than another. For example, there were no reports involving edoxaban or betrixaban, presumably because of their later approval and more limited market share.

Risk Reduction Strategies

Organizations and healthcare facilities can strive to identify system-based causes of errors involving oral anticoagulant agents and implement risk reduction strategies to prevent harm to patients. Providing education is commonly recommended to prevent errors, but this strategy, while important, is less reliable because it is heavily influenced by individual performance. System-based improvements such as constraints and standardization are more effective and produce results with less variability.^{18,19} Consider the strategies described below, which are based on a review of current literature, events submitted to the Authority, and observations from the Institute for Safe Medication Practices (ISMP).

Clinical Patient Information

- When an oral anticoagulant is indicated, before initiating therapy, collect and make readily available baseline patient information including patient weight (in metric units) and laboratory test results such as renal and liver function.^{2,6,12,19-23}
- When a patient is admitted on oral anticoagulation medications, including DOACs, include the indication and how long the patient has been on the medication(s) in the medication reconciliation note.²⁴

Drug Information

- Employ and optimize clinical decision support and approved, standardized order sets in computerized order entry and pharmacy information systems to help providers make the best treatment selection. Avert dosing errors, treatment duplication, and laboratory value interactions by firing alerts to users.^{18,19}
- Functional drug alerts, such as hard stops, that prevent a provider from ordering two anticoagulants at a time without giving a reason may prevent duplication of therapy.^{19,25}
- Ensure anticoagulation clinical decision support and protocols, including oral anticoagulant reversal protocols, are up to date. Consider proactively developing protocols even if the product is not on the organization's formulary, in anticipation of a patient being admitted on a DOAC or a patient being admitted due to an adverse event with a nonformulary medication.¹⁹

- Oral anticoagulants are sometimes involved in complex drug regimens, with risks for drug interactions or duplications. A pharmacist's review of each medication order prior to dispensing could help with verifying the drug and dose against the therapeutic indication.^{19,23,26}

Communication of Drug Orders and Other Drug Information

- Establish a process for changing anticoagulants with particular focus on preventing additional and missed doses. Having only one active order with clear annotation of when one medication should be stopped and the other is to be started in both computer systems and medication administration records (MARs) may help minimize errors.^{19,24,27}
- Establish a standard process for bridging anticoagulants during the perioperative period. Use protocols to guide therapy and reduce the risk of the improper selection of agents when initiating or changing anticoagulant therapy, including transitions from injectable products to a DOAC.²⁸⁻³⁰ Design protocols to protect against unnecessary bridging when starting a DOAC.
- Establish standard protocols for rapid or emergency reversal of anticoagulation and when to restart anticoagulant therapy.^{9,19}

Staff Competency and Education

- Annual competency assessments for clinicians who prescribe, dispense, or administer oral anticoagulants help to ensure clinicians understand different oral anticoagulant medications, differences in dosing regimens, and their indications.^{19,23}
- When a new anticoagulant is added to the organization's formulary, notify staff using tools such as newsletters and in-services. Studies show that even with continuous offerings for educational programs on therapeutic agents, healthcare professionals find it difficult to keep completely up to date through independent effort. Therefore, providing relevant and reliable information at the time that it is needed for patient care may be helpful.^{19,31}

Patient Education

- Patient counseling and education provides an opportunity to empower patients to recognize, intercept, and prevent errors. At the onset of therapy and prior to discharge, provide education to patients who are on anticoagulants. Remind patients that the risks of anticoagulants include hemorrhaging but that there are also risks of clotting from their underlying condition due to inadequate anticoagulation when doses are missed.^{19,32}

Quality Processes and Risk Management

- Define patient symptoms and condition changes, such as sudden decline in renal function, hemorrhaging, or hypercoagulability, that correlate to an ADE. Using decision support to monitor these triggers can help identify the potential or actual onset of new ADEs.^{19,33}
- When errors happen, investigate and share results with other clinicians to raise awareness about issues surrounding oral anticoagulants.^{19,27}
- Sharing success stories as well as potential, near-miss, and harmful event reports may help facilities identify possible errors and areas for improvement.^{19,27}

Conclusion

For every seven DOAC medication errors, you can expect one to result in patient harm. While safer than warfarin, DOACs should not be thought of as risk-free anticoagulants.³⁴ Similar to published data for warfarin, analysts found hemorrhages were the most common adverse event involving DOACs noted in reports submitted to the Authority. Also, the patient's age appeared to be a predominant risk factor: reports submitted to the Authority showed that 38.6% of patient harm occurred in patients 80 years of age or older. Finally, additional effort is needed to address therapeutic duplication errors, because this was the most commonly reported event category regardless of whether harm occurred.

Notes

1. Barnes GD, Lucas E, Alexander GC, Goldberger ZD. National trends in ambulatory oral anticoagulant use. *Am J Med.* 2015 Dec;128(12):1300-5.e2. Also available: <http://dx.doi.org/10.1016/j.amjmed.2015.05.044> (<http://dx.doi.org/10.1016/j.amjmed.2015.05.044>). PMID: 26144101.
2. Label: ELIQUIS- apixaban tablet, film coated. In: DailyMed [internet]. Bethesda (MD): National Library of Medicine (NLM), National Institutes of Health (NIH); 2017 Apr 24 [accessed 2017 Nov 22]. [4 p]. Available: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e9481622-7cc6-418a-acb6-c5450daae9b0> (<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e9481622-7cc6-418a-acb6-c5450daae9b0>).
3. Kreutz R, Haas S, Holberg G, Lassen MR, Mantovani LG, Schmidt A, Turpie AG. Rivaroxaban compared with standard thromboprophylaxis after major orthopaedic surgery: co-medication interactions. *Br J Clin Pharmacol.* 2016 Apr;81(4):724-34. Also available: <http://dx.doi.org/10.1111/bcp.12836> (<http://dx.doi.org/10.1111/bcp.12836>). PMID: 26580706.
4. Trkulja V. Safety of apixaban for venous thromboembolism prophylaxis: the evidence to date. *Drug Healthc Patient Saf.* 2016;8:25-38. Also available: <http://dx.doi.org/10.2147/DHPS.S74410> (<http://dx.doi.org/10.2147/DHPS.S74410>). PMID: 26937206.
5. Messori A, Fadda V, Maratea D, Trippoli S, Marinai C. Testing the therapeutic equivalence of novel oral anticoagulants for thromboprophylaxis in orthopedic surgery and for prevention of stroke in atrial fibrillation. *Int J Clin Pharmacol Ther.* 2015 Mar;53(3):211-9. Also available: <http://dx.doi.org/10.5414/CP202183> (<http://dx.doi.org/10.5414/CP202183>). PMID: 25295718.
6. Kearon C, Akl EA, Ornelas J, Blaivas A, Jimenez D, Bounameaux H, Huisman M, King CS, Morris TA, Sood N, Stevens SM, Vintch JR, Wells P, Woller SC, Moores L. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. *Chest.* 2016 Feb;149(2):315-52. Also available: <http://dx.doi.org/10.1016/j.chest.2015.11.026> (<http://dx.doi.org/10.1016/j.chest.2015.11.026>). PMID: 26867832.
7. Section 5: anticoagulants. In: Office of Disease Prevention and Health Promotion. National action plan for adverse drug event prevention. Washington (DC): U.S. Department of Health and Human Services; 2014. p. 50-98. Also available: <https://health.gov/hcq/pdfs/ADE-Action-Plan-Anticoagulants.pdf> (<https://health.gov/hcq/pdfs/ADE-Action-Plan-Anticoagulants.pdf>).
8. Baker WL, Cios DA, Sander SD, Coleman CI. Meta-analysis to assess the quality of warfarin control in atrial fibrillation patients in the United States. *J Manag Care Pharm.* 2009 Apr;15(3):244-52. Also available:

- <http://dx.doi.org/10.18553/jmcp.2009.15.3.244> (<http://dx.doi.org/10.18553/jmcp.2009.15.3.244>). PMID: 19326955.
9. Institute for Safe Medication Practices (ISMP). 2016 Q4 - annual report. QuarterWatch. Horsham (PA): Institute for Safe Medication Practices (ISMP); 2017 Jul 12. 25 p. Also available: <https://www.ismp.org/quarterwatch/annual-report-2016> (<https://www.ismp.org/quarterwatch/annual-report-2016>).
 10. Shehab N, Lovegrove MC, Geller AI, Rose KO, Weidle NJ, Budnitz DS. US emergency department visits for outpatient adverse drug events, 2013-2014. *JAMA*. 2016 Nov 22;316(20):2115-25. Also available: <http://dx.doi.org/10.1001/jama.2016.16201> (<http://dx.doi.org/10.1001/jama.2016.16201>). PMID: 27893129.
 11. Kundu A, Sardar P, Chatterjee S, Aronow WS, Owan T, Ryan JJ. Minimizing the risk of bleeding with NOACs in the elderly. *Drugs Aging*. 2016 Jul;33(7):491-500. Also available: <http://dx.doi.org/10.1007/s40266-016-0376-z> (<http://dx.doi.org/10.1007/s40266-016-0376-z>). PMID: 27174293.
 12. You JJ, Singer DE, Howard PA, Lane DA, Eckman MH, Fang MC, Hylek EM, Schulman S, Go AS, Hughes M, Spencer FA, Manning WJ, Halperin JL, Lip GY, American College of Chest Physicians. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012 Feb;141(2 Suppl):e531S-75S. PMID: 22315271.
 13. Harper P, Young L, Merriman E. Bleeding risk with dabigatran in the frail elderly. *N Engl J Med*. 2012 Mar 01;366(9):864-6. Also available: <http://dx.doi.org/10.1056/NEJMc1112874> (<http://dx.doi.org/10.1056/NEJMc1112874>). PMID: 22375994.
 14. Atrial fibrillation fact sheet. [internet]. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2017 Aug 22 [accessed 2018 May 24]. [5 p]. Available: https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_atrial_fibrillation.htm (https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_atrial_fibrillation.htm).
 15. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med*. 2011 Nov 24;365(21):2002-12. PMID: 22111719.
 16. Hellenbart EL, Faulkenberg KD, Finks SW. Evaluation of bleeding in patients receiving direct oral anticoagulants. *Vasc Health Risk Manag*. 2017;13:325-42. Also available: <http://dx.doi.org/10.2147/VHRM.S121661> (<http://dx.doi.org/10.2147/VHRM.S121661>). PMID: 28860793.
 17. Lip GY, Pan X, Kamble S, Kawabata H, Mardekian J, Masseria C, Bruno A, Phatak H. Major bleeding risk among non-valvular atrial fibrillation patients initiated on apixaban, dabigatran, rivaroxaban or warfarin: a "real-world" observational study in the United States. *Int J Clin Pract*. 2016 Sep;70(9):752-63. Also available: <http://dx.doi.org/10.1111/ijcp.12863> (<http://dx.doi.org/10.1111/ijcp.12863>). PMID: 27550177.
 18. Institute for Safe Medication Practices (ISMP). ISMP medication safety self assessment for antithrombotic therapy - frequently asked questions (FAQs). Horsham (PA): Institute for Safe Medication Practices (ISMP); 2017. 5 p. Also available: <https://www.ismp.org/sites/default/files/attachments/2017-11/ISMP128-Antithrombotic%20FAQ-021017.pdf> (<https://www.ismp.org/sites/default/files/attachments/2017-11/ISMP128-Antithrombotic%20FAQ-021017.pdf>).

19. Andreica I, Grissinger M. Oral anticoagulants: a review of common errors and risk reduction strategies. *Pa Patient Saf Advis*. 2015 Jun;12(2):54-61. Also available: http://patientsafety.pa.gov/ADVISORIES/Pages/201506_54.aspx (http://patientsafety.pa.gov/ADVISORIES/Pages/201506_54.aspx).
20. Label: PRADAXA- dabigatran etexilate mesylate capsule. In: DailyMed [internet]. Bethesda (MD): National Library of Medicine (NLM), National Institutes of Health (NIH); 2017 Aug 15 [accessed 2017 Nov 22]. [5 p]. Available: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ba74e3cd-b06f-4145-b284-5fd6b84ff3c9> (<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=ba74e3cd-b06f-4145-b284-5fd6b84ff3c9>).
21. Label: XARELTO- rivaroxaban tablet, film coated. XARELTO- rivaroxaban. In: DailyMed [internet]. Bethesda (MD): National Library of Medicine (NLM), National Institutes of Health (NIH); 2017 Nov 6 [accessed 2017 Nov 22]. [4 p]. Available: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=10db92f9-2300-4a80-836b-673e1ae91610> (<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=10db92f9-2300-4a80-836b-673e1ae91610>).
22. Label: SAVAYSA- edoxaban tosylate tablet, film coated. In: DailyMed [internet]. Bethesda (MD): National Library of Medicine (NLM), National Institutes of Health (NIH); 2017 Nov 6 [accessed 2017 Nov 22]. [4 p]. Available: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e77d3400-56ad-11e3-949a-0800200c9a66> (<https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e77d3400-56ad-11e3-949a-0800200c9a66>).
23. High-alert medication feature: anticoagulant safety takes center stage in 2007. *ISMP Med Saf Alert Acute Care*. 2007 Jan;12(1):1-3. Also available: <https://www.ismp.org/resources/high-alert-medication-feature-anticoagulant-safety-takes-center-stage-2007> (<https://www.ismp.org/resources/high-alert-medication-feature-anticoagulant-safety-takes-center-stage-2007>).
24. Armor BL, Wight AJ, Carter SM. Evaluation of adverse drug events and medication discrepancies in transitions of care between hospital discharge and primary care follow-up. *J Pharm Pract*. 2016 Apr;29(2):132-7. Also available: <http://dx.doi.org/10.1177/0897190014549836> (<http://dx.doi.org/10.1177/0897190014549836>). PMID: 25312264.
25. Institute for Safe Medication Practices (ISMP). ISMP medication safety self assessment for antithrombotic therapy. Horsham (PA): Institute for Safe Medication Practices (ISMP); 2017. 26 p. Also available: <https://www.ismp.org/sites/default/files/attachments/2017-11/ISMP128-Antithrombotic%20SA-021017.pdf> (<https://www.ismp.org/sites/default/files/attachments/2017-11/ISMP128-Antithrombotic%20SA-021017.pdf>).
26. Burnett AE, Mahan CE, Vazquez SR, Oertel LB, Garcia DA, Ansell J. Guidance for the practical management of the direct oral anticoagulants (DOACs) in VTE treatment. *J Thromb Thrombolysis*. 2016 Jan;41(1):206-32. Also available: <http://dx.doi.org/10.1007/s11239-015-1310-7> (<http://dx.doi.org/10.1007/s11239-015-1310-7>). PMID: 26780747.
27. Cohen MR. Medication errors. 2nd ed. Washington (DC): American Pharmacists Association; 2007. Chapter 9: Preventing prescribing errors.
28. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R. Perioperative management of antithrombotic therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012 Feb;141(2 Suppl):e326S-50S. PMID: 22315266.
29. Spyropoulos AC, Al-Badri A, Sherwood MW, Douketis JD. Periprocedural management of patients receiving a vitamin K antagonist or a direct oral anticoagulant requiring an elective procedure or surgery. *J Thromb*

- Haemost. 2016 May;14(5):875-85. Also available: <http://dx.doi.org/10.1111/jth.13305> (<http://dx.doi.org/10.1111/jth.13305>). PMID: 26988871.
30. Shaw J, de Wit C, Le Gal G, Carrier M. Thrombotic and bleeding outcomes following perioperative interruption of direct oral anticoagulants in patients with venous thromboembolic disease. *J Thromb Haemost.* 2017 May;15(5):925-30. Also available: <http://dx.doi.org/10.1111/jth.13670> (<http://dx.doi.org/10.1111/jth.13670>). PMID: 28296069.
 31. Routledge PA, O'Mahony MS, Woodhouse KW. Adverse drug reactions in elderly patients. *Br J Clin Pharmacol.* 2004 Feb;57(2):121-6. PMID: 14748810.
 32. New oral anticoagulants for acute venous thromboembolism. *JAMA.* 2014 Feb 19;311(7):731-2. Also available: <http://dx.doi.org/10.1001/jama.2014.202> (<http://dx.doi.org/10.1001/jama.2014.202>). PMID: 24549554.
 33. Rozich JD, Haraden CR, Resar RK. Adverse drug event trigger tool: a practical methodology for measuring medication related harm. *Qual Saf Health Care.* 2003 Jun;12(3):194-200. PMID: 12792009.
 34. Hanley CM, Kowey PR. Are the novel anticoagulants better than warfarin for patients with atrial fibrillation? *J Thorac Dis.* 2015 Feb;7(2):165-71. Also available: <http://dx.doi.org/10.3978/j.issn.2072-1439.2015.01.23> (<http://dx.doi.org/10.3978/j.issn.2072-1439.2015.01.23>). PMID: 25713732.
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