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AN ONGOING CE PROGRAM
of the University of Connecticut
School of Pharmacy

EDUCATIONAL OBJECTIVES

After participating in this activity pharmacists will be able to:

- Describe the burden of illness from anticoagulant-associated severe bleeding
- Identify high-risk factors in DOAC-associated bleeding, including intracranial hemorrhage, GI bleeding and critical area or organ
- Describe reversal treatments for DOAC-associated bleeds
- Apply guidelines for reversing DOACs
- Discuss patient evaluation and institutional protocol concepts for DOAC reversal

After participating in this activity pharmacists and pharmacy technicians will be able to:

- Discover resources for patient information on anticoagulation and bleeding risk
- Identify the medications used in DOAC anticoagulation therapy
- Recall the medications used to reverse DOAC anticoagulation therapy
- Determine when to refer the patient to the pharmacist regarding DOAC anticoagulation therapy

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Pharmacists and pharmacy technicians are eligible to participate in this application-based activity and will receive up to 0.2 CEU (2 contact hours) for completing the activity, passing the quiz with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

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DOAC-Associated Bleeding: Risks and Reversal Strategies

ABSTRACT: The use of direct oral anticoagulants (DOACs) for the treatment and prevention of thromboembolic events has steadily increased. The DOACs offer an improved risk/benefit profile with regard to their comparable efficacy and decreased risk of bleeding compared to vitamin K antagonists. Despite their association with decreased risks of major bleeding, DOACs, as with all anticoagulant medications, put patients at risk of bleeding. Until recently, one advantage vitamin K antagonists possessed over DOACs was a drug-specific antidote to reverse their anticoagulant effects. The development of idarucizumab for dabigatran and andexanet alfa for rivaroxaban and apixaban has partially addressed this need. However, there is still no FDA-approved reversal agent for edoxaban or betrixaban. Furthermore, clinicians must consider key differences at the individual patient level regarding bleeding risk and management. The American College of Cardiology recently published a consensus decision pathway to help guide the management of oral anticoagulant-associated bleeding. This pathway is a useful tool in the management of DOACs, but the topic of DOAC-associated bleeding is a rapidly evolving topic, with new data becoming available, and further reversal agents in the pipeline.

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INTRODUCTION

The Centers for Disease Control and Prevention (CDC) +-estimates that more than 900,000 venous thromboembolism (VTE) events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), occur in the United States (US) annually. VTE is associated with high recurrence and mortality rate (60,000-100,000 Americans die from VTE each year).[1] Additionally, approximately 2.7 million people in the US have nonvalvular atrial fibrillation (NVAF; see **Sidebar**, page 2) with the prevalence expected to grow to 12.1 million by 2030.[2] Patients with atrial fibrillation are at an increased risk of stroke and systemic thromboembolic events.

Pause and Ponder:
How many of your patients are taking direct oral anticogulants? What are the most common indications?

Anticoagulation is the mainstay of therapy for prevention and treatment of VTE and prevention of thromboembolic stroke in patients with AF. Anticoagulation is associated with more than a 90% reduction in the rate of recurrence of VTE[3] and reduces the risk of stroke 4- to 5-fold in patients with NVAF.[2] Oral anticoagulants offer patients the convenience of taking an anticoagulation medication in the outpatient setting without the need for intravenous or subcutaneous injections as needed with unfractionated and low molecular weight heparins.

Historically, clinicians have used vitamin K antagonists, such as warfarin, as the primary option for oral anticoagulation. While effective, vitamin K antagonists are not without shortcomings. Studies show that direct oral anticoagulants (DOACs) are at least as effective as vitamin K antagonists in the treatment of VTE and stroke prevention in NVAF, and reduce the risk of bleeding, especially intracranial hemorrhage (ICH).[4-11] DOACs also offer several advantages over vitamin K antagonists including

- rapid onset of action and predictable pharmacokinetic profiles,
- wide therapeutic windows eliminating the need for laboratory monitoring, and
- fewer drug-drug and drug-food interactions.

Epidemiologists estimate that at any point in time, prescribers are treating more than six million patients with anticoagulants in the US, with DOAC use trending upwards.[12] While DOACs offer advantages over their vitamin K antagonist counterparts, they still introduce an increased risk of bleeding for patients; managing DOAC-associated bleeding is vital to minimizing major adverse and fatal events. Almost all patients who take DOACs receive them from community pharmacies, but clinicians treat almost all DOAC-associated bleeds in inpatient settings. The pharmacy team is the first line of defense against DOAC-associated bleeds in the community (see **Sidebar** on page 3), and vital to timely response at the hospital. The primary focus of this activity is DOAC-associated bleeding, but an introduction to the nuances of oral anticoagulation is needed to fully understand management of DOAC-associated bleeding.

ANTICOAGULANT MEDICATIONS

Vitamin K antagonists exert their anticoagulant effects through inhibition of vitamin K-dependent clotting factors in the liver. By inhibiting vitamin K, several factors, including clotting factor II (thrombin), VII, IX, and X, which disrupts the final common pathway of the clotting cascade, are affected (**Figure 1**). Vitamin K antagonists display a variable and prolonged time to onset and offset due to the long half-lives of these vitamin K-dependent clotting factors. Dabigatran is a direct thrombin inhibitor, and rivaroxaban, apixaban, edoxaban, and betrixaban directly inhibit activated clotting factor X (FXa) activity. Direct action on target-specific clotting factors allows DOACs to have a rapid onset and more predictable anticoagulant effects.[13]

SIDEBAR: Atrial fibrillation is a type of irregular heartbeat that occurs when the two upper chambers of the heart beat irregularly and rapidly. Consistent, steady blood flow is important because stagnant pools of blood are prone to forming clots. Fibrillating heartbeats cause blood to flow abnormally and collect in areas of the heart. One area that is prone to forming clots is the left atrial appendage. In patients with atrial fibrillation, erratic blood flow causes a pool of blood to collect and sit in the left atrial appendage. A thrombus, or blood clot, forms in this pool of stagnant blood and then reenters the blood stream. When the heart pumps to supply blood to organs, such as the brain, the clot travels in the blood. If the clot travels to the brain and blocks blood and oxygen to an area of the brain, the patient experiences a stroke. Anticoagulation is important in preventing strokes in patients with atrial fibrillation as it helps prevent thrombus formation a when the heart beats irregularly.

Direct Oral Anticoagulants

The Food and Drug Administration (FDA) first approved dabigatran, the direct thrombin inhibitor, in 2010.[14] The factor Xa inhibitors have been FDA-approved for various indications (**Table 1,** page 4) with rivaroxaban, apixaban, edoxaban, and betrixaban receiving initial approval in 2011, 2012, 2015, and 2017, respectively.[15-18]

Important pharmacokinetic and pharmacodynamic differences exist between the DOACs (**Table 2,** page 5). Apixaban must be taken twice daily,[16] edoxaban and betrixaban once daily,[17,18] and dabigatran and rivaroxaban once or twice daily, depending on the indication.[14,15]

Renal clearance is an especially important parameter to consider when comparing DOACs. All DOACs are eliminated mainly through the kidneys, although the extent of their renal elimination varies. Most DOACs should be avoided in patients with severe renal dysfunction. However, betrixaban relies on the kidneys for elimination the least of all the DOACs and requires a dose adjustment for creatinine clearance (CrCl) of 15-30 mL/min.[18] Conversely, edoxaban is not recommended for use in patients with severe renal dysfunction or in those with NVAF with CrCl exceeding 95 mL/min.[17] Additionally, dabigatran is the only DOAC that is dialyzable, which is an important consideration in its management in the setting of overdose and/or bleeding reversal.[19]

SIDEBAR: DOAC-associated Bleeding: Prevention is the Best Medicine

The best way to prevent DOAC-associated bleeding is to educate patients early, often, and thoroughly. Pharmacy staff needs to form strong alliances with patients who fill prescriptions for anticoagulants, and touch base each time patients refill prescriptions. Keeping a few important points in mind can increase the margin of safety:

- Patients take anticoagulants for a variety of indications. Many patients have VTE of unknown origins, atrial fibrillation, or cancer. Know your patient's indications for anticoagulation, and refer them to disease-specific web sites. Blue Cross, Blue Shield, and Blue Care Network of Michigan provides an Anticoagulation Toolkit that is a handy reference. Find it here: http://www.anticoagulationtoolkit.org/sites/default/files/toolkit_pdfs/toolkitfull.pdf.
- The FDA has mandated that drug companies include a Medication Guide for all of the DOACs (dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban). The FDA requires pharmacy staff to issue Medication Guides with each new prescription or refill. The drug company updates the Medication Guide periodically, so pharmacists and technicians should use the most current iteration. The drug company includes the Medication Guide with the product. Pharmacy staff can also find and print the most current version at https://www.fda.gov/drugs/drug-safety-and-availability/medication-guides.
- Staff should review the Medication Guide with patients at least annually, and ask questions each time patients refill prescriptions. Each DOAC has a web site that can provide information in a different way, and referring patients to the web site is a good step. Note that dabigatran's US healthcare provider web site also helps clinicians find the reversal agent. (The patient and healthcare provider web sites are different.)
- Actively monitor over-the-counter drug use. In particular, nonsteroidal anti-inflammatory drugs are contraindicated. Acetaminophen is the preferred OTC analgesic, and recommending nonpharmacologic interventions like massage, heat or cold, exercise, and weight loss can help.
- Americans use complementary and alternative medications with remarkable frequency, and are often forgetful about or reluctant to disclose their use. Patients who take apixiban should avoid grapefruit juice. Studies suggest that four supplements are likely to interact with DOACs, and all DOAC patients should avoid the following supplements:
    - Cocoa can inhibit platelet adhesion, aggregation, and activity. Theoretically, cocoa may increase bleeding risk when used with other antiplatelet or anticoagulant drugs.
    - Danshen, a Chinese herb that is used for circulation problems (ischemic stroke, chest pain, atherosclerosis), high cholesterol, high blood pressure, heart attack, cardiovascular disease, and a host of other indications, has been reported to have antithrombotic effects.
    - St. John's wort, a supplement used for depression, anxiety, and insomnia, induces P-glycoprotein.
    - Willow bark, also called nature's aspirin, has antiplatelet effects.

Other herbals may interact with DOACs. Pharmacy staff can find reliable information about interactions with supplements at the Natural Medicines Therapeutic Research site (https://naturalmedicines.therapeuticresearch.com/)

Figure 1. Site of Action of Oral Anticoagulants

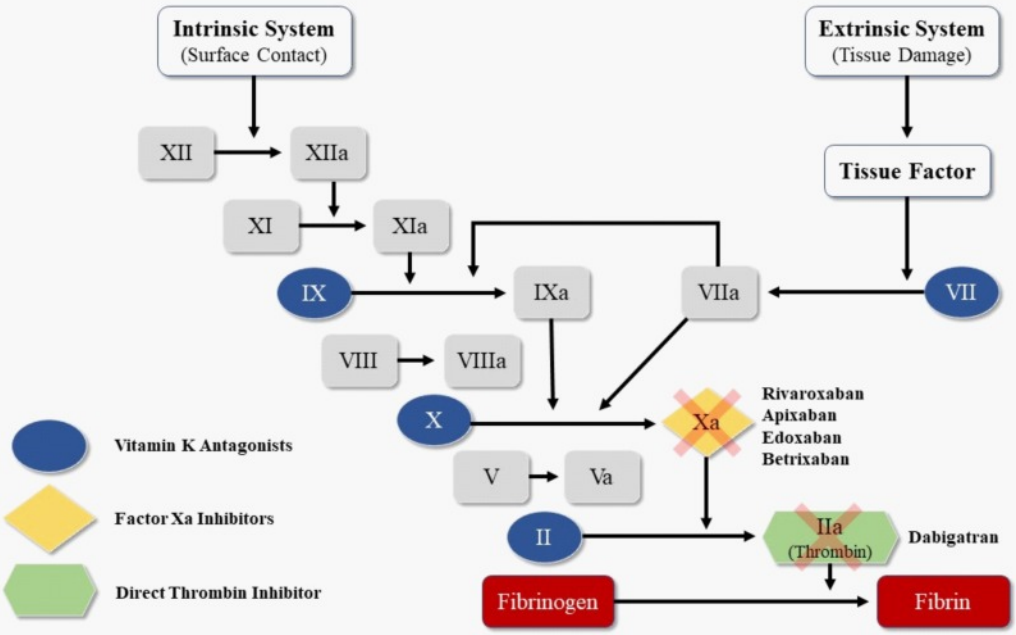

Table 1. FDA Approved Indications and Dosing of DOACs[14-18]

	Direct Thrombin (Factor IIa) Inhibitor	Direct Factor Xa Inhibitors			
	Dabigatran	**Rivaroxaban**	**Apixaban**	**Edoxaban**	**Betrixaban**
FDA Approved Indications and Dosages	**NVAF** ▪ CrCl >30 mL/min: 150 mg PO BID ▪ CrCl 15-30 mL/min: 75 mg PO BID ▪ CrCl <15 mL/min: **not recommended** **VTE treatment** ▪ CrCl >30 mL/min: 150 mg PO BID after 5-10 days of parenteral anticoagulation **VTE secondary prevention** ▪ CrCl >30 mL/min: 150 mg BID after previous treatment **VTE prophylaxis in total hip replacement** ▪ CrCl >30 mL/min: 110 mg PO firsts day; then 220 mg PO daily	**NVAF** ▪ CrCl >50 mL/min: 20 mg PO daily with evening meal ▪ CrCl 15-50 mL/min: 15 mg PO daily with evening meal ▪ Crcl <15 mL/min: **not recommended** **VTE treatment** ▪ 15 mg PO BID with for 21 days; followed by 20 mg PO daily with food **VTE secondary prevention** ▪ 10 mg PO daily with or without food after at least 6 months of standard anticoagulation treatment **VTE prophylaxis in total hip or knee replacement** ▪ 10 mg PO daily with or without food **Reduction of risk of major CV events in chronic CAD or PAD** ▪2.5 mg PO BID with or without food in combination with aspirin (75-100 mg) once daily	**NVAF** ▪ 5 mg PO BID ▪ 2.5 mg PO BID: if ≥2 of the following: age ≥80 years, weight ≤60 kg or SCr ≥ 1.5 mg/dL **VTE treatment** ▪ 10 mg PO BID for 7 days; followed by 5 mg PO BID **VTE secondary prevention** ▪ 2.5 mg PO BID **VTE prophylaxis in total hip or knee replacement** ▪ 2.5 mg PO BID	**NVAF** ▪ CrCl >95 mL/min: **not recommended** ▪ CrCl >50-95 mL/min: 60 mg PO daily ▪ CrCl 15-50 mL/min: 30 mg PO daily **VTE treatment** ▪ CrCl >50 mL/min: 60 mg PO daily CrCl 15-50 mL/min or body weight ≤60 kg or who use certain P-gp inhibitors: 30 mg once daily	**VTE prophylaxis in hospitalized patients with acute medical illness** ▪160 mg PO once; followed by 80 mg once daily taken at the same time each day with food

Table 2. Pharmacokinetic Properties of DOACs[14-18]

	Direct Thrombin (Factor IIa) Inhibitor	Direct Factor Xa Inhibitors			
Properties	**Dabigatran**	**Rivaroxaban**	**Apixaban**	**Edoxaban**	**Betrixaban**
Bioavailability (%)	3 to 7	80-100 (2.5 and 10 mg dose) 66 (20 mg dose)	50	62	34
Crushable	No ▪ Oral bioavailability increases by 75% when pellets are taken without capsule Capsules should not be broken, chewed, or opened	Oral administration of crushed tablets in applesauce Nasogastric tube administration of crushed tablets suspended in water (avoid administration distal to stomach)	Oral administration of crushed tablets in 30 mL of water Nasogastric tube administration of crushed tablets in 60 mL of D5W	No	No data on opening capsules
T-Max (hr)	1 to 3 (delayed by food)	2 to 4	3 to 4	1 to 2	3 to 4
Half-life (hr)	12 to 17	5 to 9	12	10 to 14	19 to 27
Renal Elimination (%)	80	36	27	50	11
Key Drug Interactions	P-gp inducers ▪ Avoid use P-gp inhibitors and CrCl 30-50 mL/min ▪ Reduce dose to 75 mg PO BID if administered with dronedarone or ketoconazole P-gp inhibitors and CrCl 15-30 mL/min Avoid use	Combined potent P-gp and CYP3A4 inducers or inhibitors Avoid use	Combined potent P-gp and CYP3A4 inhibitors ▪ 5 or 10 mg dose: decrease dose by 50% ▪ 2.5 mg dose: avoid use Combined potent P-gp and CYP3A4 inducers Avoid use	Potent P-gp inducers and inhibitors ▪Avoid concomitant use with rifampin	Potent P-gp inhibitors ▪80 mg PO once; followed by 40 mg PO daily

Oral bioavailability also varies among the DOACs. Dabigatran is administered as a prodrug to increase its bioavailability. Rivaroxaban has varying bioavailability depending on the dose. The 10 mg dose has the highest bioavailability at 80%. However, with the 20 mg dose, its bioavailability is approximately 66% and the product labeling recommends administering it with food to enhance oral absorption.[15] Rivaroxaban and apixaban can also be crushed and administered as solutions,[15,16] while dabigatran capsules cannot be opened or chewed as this is increases dabigatran's bioavailability by 75%.[14]

DOACs have fewer drug-drug interactions than vitamin K antagonists, but there are important interactions worth recognizing. All DOACs are substrates of the P-glycoprotein (P-gp) transporter. Drug interactions with dabigatran, edoxaban, and betrixaban are primarily driven by the P-gp transport system. Product labeling recommends dose reductions for each of these agents if used concomitantly with strong P-gp inhibitors.[14,17,18] Rivaroxaban and apixaban are additionally affected by the CYP3A4 system. Concomitant use of rivaroxaban with strong dual inducers or inhibitors of P-gp and CYP3A4 is contraindicated.[15] Apixaban requires a dose reduction when used with strong dual inducers or inhibitors of both P-gp and CYP3A4.[16]

Table 3. Risk Factors for DOAC-Related Bleeding[26-28]

- Advanced age
- Alcohol abuse
- Anemia
- Falling or elevated fall risk
- History of stroke or bleeding
- Hypertension
- Impaired renal or hepatic function
- Malignancy
- Thrombocytopenia
- Use of antiplatelet or nonsteroidal anti-inflammatory medications

ADVERSE DRUG EFFECTS OF ANTICOAGULANTS

DOACs are mostly associated with less major bleeding compared to vitamin K antagonists[20-22] and betrixaban displayed similar rates of bleeding compared to the low molecular weight heparin enoxaparin.[23] DOACs significantly reduce the relative risk of ICH however, higher rates of major GI bleeding are seen with the DOACs compared to vitamin K antagonists.[24]

Although DOACs are associated with lower rates of major bleeding compared to other anticoagulant therapies for prevention and treatment of VTE and stroke prevention in NVAF, the risk for major bleeding events still exists with these drugs. Major GI bleeds are more common with DOACs than vitamin K antagonists. Additionally, although less common, DOAC-associated major bleeding episodes can be fatal.[25]

Patient Specific Risk Factors

Individualization of therapy is an important factor in minimizing the risk of bleeding in patients on anticoagulation. Several validated scoring systems exist to assess the risk of bleeding in patients with NVAF. The HAS-BLED (https://www.mdcalc.com/has-bled-score-major-bleeding-risk), ATRIA (https://www.mdcalc.com/atria-bleeding-risk-score), and HEMORR$_2$HAGES (https://www.mdcalc.com/hemorr2hages-score-major-bleeding-risk) bleeding risk scores have demonstrated the ability to predict clinically relevant bleeding.[26-28] Each of the three bleeding risk prediction scores provide insight into patient factors associated with an increased bleeding risk (**Table 3**).

Tech Talk: What is P-GP?

P-glycoprotein is an efflux protein embedded in cell membranes that pumps toxins and xenobiotics (foreign chemical substances) out of cells. It plays an important role in the absorption of drugs as many drugs are substrates of the P-gp system. This means P-gp facilitates drug uptake into cells. Interference with P-gp can affect the absorption and action of drugs.

- P-gp inhibition leads to increased bioavailability and effect.
- Induction leads to decreased bioavailability and effect of drugs affected by P-gp.

The cytochrome P450 or CYP450 system is a large system of enzymes involved in the metabolism of substances. The enzymes are numbered by the specific family they belong to depending on their mode of action. CYP3A4 is the primary family involved in drug metabolism most commonly found in the liver and intestines. Inhibition or induction of these enzymes can affect drug metabolism and subsequently their therapeutic or toxic effects similarly to P-gp.

- Inhibitors of the CYP system reduce the metabolism of drugs affected by the system, increasing their concentrations and thus the drugs' effects.
- The reverse is true for CYP system induction.

PAUSE AND PONDER: How closely do you monitor for DOAC-associated drug interactions? If you override alerts, what criteria do you use to decide which to pursue and which to override?

Pharmacokinetic Interactions

P-gp transport proteins mediate DOAC absorption. P-gp inhibitors, therefore, potentially increase DOAC absorption and effect. P-gp inducers potentially decrease absorption and effect. In the same regard, strong CYP3A4 inhibitors potentially decrease the metabolism of rivaroxaban and apixaban, increasing their effect. Conversely strong CYP3A4 inducers potentially increase their metabolism, decreasing their anticoagulant effect.

Possible drug interactions, especially when combined with other clinical risk factors affecting DOAC plasma levels, are important factors for choosing specific DOACs for specific patients**.** Clinicians typically treat patients with NVAF with a variety of cardiovascular drugs (e.g. verapamil, dronedarone) that may interact with an anticoagulation regimen .[29-31] It is also important to consider drug interactions in patients taking natural products. Purity and potency of over-the-counter supplements and natural products are highly variable, so evaluation of a patient's complete medication history is important. Products that are known to be strong P-gp and CYP3A4 inhibitors and inducers, such as St. Johns Wort, should be avoided in patients taking DOACs.[15]

Pharmacodynamic Interactions

Pharmacodynamic considerations likewise need to be considered in patients receiving DOACs. Co-administration of DOACs with other anticoagulants, antiplatelets, and non-steroidal anti-inflammatory drugs (NSAIDs) further increases a patient's risk of bleeding. DOACs should not be administered with other anticoagulants. Clinicians should be cautious with patients receiving antiplatelet medications and/or NSAIDs, limiting co-administration of these medications to the shortest possible duration.[31] If patients require an analgesic medication, acetaminophen is preferred over NSAIDs.

Although antiplatelet agents should be avoided when possible, a complex clinical scenario exists in patients with NVAF and coronary artery disease (CAD). Adding dual antiplatelet therapy (DAPT), and even a single antiplatelet agent on top of a DOAC, increases the risk of bleeding.[31] This creates a clinical conundrum, as DAPT is necessary to prevent stent thrombosis in patients with CAD after percutaneous coronary intervention (PCI). But DAPT alone is inferior to anticoagulation for stroke prevention in NVAF, seemingly necessitating the need for both according to current evidence. Current NVAF guidelines recommend the use of clopidogrel with rivaroxaban 15 mg daily or dabigatran 150 mg daily if a DOAC is needed.[32] Guidelines also recommend limiting the duration of triple therapy, if needed, to four to six weeks, then transitioning to double therapy.[32]

Strategies to minimize bleeding risk factors in patients receiving DOACs include

- controlling blood pressure
- dosing appropriately according to age, weight and renal function
- minimizing alcohol intake, and
- avoiding or limiting the duration of co-administration of drugs that increase bleeding risk (e.g. NSAIDS, antiplatelet medications, and inhibitors of the P-gp and CYP3A4 systems).

TREATMENT OF DOAC-ASSOCIATED BLEEDING

When DOACs were initially introduced, a major disadvantage was the lack of a specific antidote to reverse their anticoagulation effects. Strategies to manage bleeding, depending on bleeding severity and setting, may vary. Clinicians have employed hemodialysis for dabigatran removal, clotting factor concentrates, and activated charcoal in DOAC-associated bleeding events, although the evidence is mostly limited to small case series.[33-35] In October 2015, the FDA approved idaruzicumab as an antidote to reverse dabigatran's anticoagulant effects.[36] In May 2018, the FDA approved the factor Xa reversal agent andexanet alfa for rivaroxaban and apixaban reversal.[37]

Idarucizumab

Idarucizumab is a humanized monoclonal antibody fragment (Fab) indicated in patients treated with dabigatran for the reversal of its anticoagulant effects. It works by binding to dabigatran and its metabolites with an affinity approximately 350 times greater than the binding affinity of dabigatran to thrombin. Due to its higher binding affinity, idarucizumab is expected to reverse the activities of free, unbound, and thrombin-bound drug. Additionally, idarucizumab only has affinity for dabigatran and cannot be used to reverse other anticoagulants' effects.[36]

Idarucizumab is currently approved for dabigatran reversal in the setting of emergency surgery or urgent procedures and in life-threatening uncontrolled bleeds. Phase 1 studies in healthy volunteers displayed dose-dependent complete reversal of dabigatran that was sustained for at least 24 hours.[38,39] The drug was well tolerated with few, only minor events reported and no evidence of immunogenicity.

The phase III RE-VERSE AD (Reversal Effects of Idarucizumab on Active Dabigatran) trial used a 5 g intravenous dose to reverse dabigatran's anticoagulant effect in patients with uncontrolled bleeding (group A) or patients who were about to undergo an urgent procedure (group B).[40] The primary endpoint was the maximum level of dabigatran reversal four hours after administration as measured by dilute thrombin time (dTT) or ecarin clotting time (ECT). In 503 patients (301 group A and 202 group B) the median maximal percentage of dabigatran reversal was

100%. In group A, 45.5% of patients presented with GI bleeds, 32.6% presented with ICH, and 25.9% had bleeding caused by trauma. Dabigatran reversal was rapid, and concentrations remained low (lower than 20 ng/mL of unbound-dabigatran) for the majority of patients for 24 hours. Recurrence of levels above 20 ng was observed in 23% of patients and was associated with continued bleeding in 10 patients in group A and none in group B. Of note, in total nine patients received more than the 5 g initial idarucizumab dose. Of 203 patients assessed in group A, 67.7% achieved confirmed bleeding cessation within 24 hours with a median time to hemostasis of 2.5 hours (95% CI: 2.2 to 3.9). Of the 197 patients assessed from group B, 93.4% were determined to have normal hemostasis at the time of procedure. Thrombotic events were rare, with 4.8% and 6.8% of the overall cohort experiencing an event at 30 and 90 days, respectively.[40]

Idarucizumab is provided in two separate 2.5 g/50 mL vials. Vials should be stored in the refrigerator and protected from light. Vials can be stored at room temperature for up to 48 hours in the original carton protected from light but must be used within six hours if exposed to light. It is administered intravenously in two consecutive infusions hanging the vials for a total dose of 5 g. Additional doses may be needed in the setting of excessively high dabigatran concentrations, although few patients received additional doses in the RE-VERSE AD trial and this practice's safety and efficacy are yet to be fully determined. Reversal of dabigatran by idarucizumab exposes patients with underlying disease states with thromboembolic risk to thromboembolic events. If deemed appropriate, dabigatran can be reinitiated in patients 24 hours after idarucizumab administration.[36] Idarucizumab is available nationwide and can be located at specific locations via the manufacturer's website (https://www.praxbind.com/find-praxbind).

Andexanet Alfa

Andexanet alfa is a genetically modified variant of human coagulation factor Xa. It acts as a decoy protein binding to and preventing the action both direct (rivaroxaban, apixaban, edoxaban, betrixaban) and indirect (enoxaparin and fondaparinux) factor Xa inhibitors. Andexanet alfa has a strong affinity for factor Xa inhibitors that overcomes the binding competition for endogenous factor Xa. This allows factor Xa to resume its normal function of activating prothrombin to thrombin within the clotting cascade. It is worth noting that at this time, despite its mechanistic activity, andexanet alfa has not been shown to be effective for, and is not indicated for, the treatment of bleeding associated with any factor Xa inhibitors other than rivaroxaban and apixaban.[37]

Andexanet alfa received accelerated approval for patients treated with rivaroxaban or apixaban when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding. This approval was based on the change from baseline in anti-FXa activity in healthy volunteers which indicated reversal of anticoagulation. At the time of approval, improvement in hemostasis had not yet been established. Andexanet alfa has been determined to have an established effect on a surrogate endpoint (percent change in anti-factor Xa activity) that is reasonably likely to provide clinical benefit. Under the FDA's accelerated approval conditions, the company must provide further evidence of clinical benefit evidenced by improvement in hemostatic outcomes.[41] Approval for this indication is contingent upon the results of the ANNEXA-4 trial which was published in April 2019.[41-43]

PAUSE AND PONDER: How can pharmacy staff ensure that in the rare case one of their patients develops a DOAC-associated bleed, he receives the reversal agent he needs?

Andexanet alfa gained approval for the reversal of the anticoagulant effects of rivaroxaban and apixaban based data of two phase III clinical trials, ANNEXA-R and ANNEXA-A (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of FXA Inhibitors Rivaroxaban and Apixaban).[44] These studies examined andexanet alfa's effect in healthy volunteers taking rivaroxaban and apixaban, respectively. The researchers gave healthy volunteers either rivaroxaban 20 mg daily for four days or apixaban 5 mg twice daily for 3.5 days. Then, they administered andexanet alfa at four hours and three hours after the last dose of DOAC, respectively. Dosing of andexanet alfa for the reversal of rivaroxaban and apixaban differed based on results from a phase II program used to establish drug dosing. For rivaroxaban reversal, the dose was an 800 mg bolus (30 mg per minute) or an 800 mg bolus followed by a continuous infusion of 8 mg per minute for 120 minutes (960 mg total). For reversal of apixaban the dose was a 400 mg bolus (30 mg per minute) or a 400 mg bolus followed by a continuous infusion of 4 mg per minute for 120 minutes (480 mg total).[44] The researchers evaluated reversal of rivaroxaban and apixaban by the percent change in anti-factor Xa activity using a validated chromogenic assay of factor Xa activity. Anti-factor Xa activity was reduced in two to five minutes and persisted for two hours, with a return of anti-factor Xa activity gradually over time. Additionally, thrombin generation was significantly greater in the andexanet alfa arm compared to placebo in the rivaroxaban and apixaban studies. No serious adverse events or thrombotic events were reported in either study.[44]

The ANNEXA-4 (Andexanet Alfa, a Novel Antidote to the Anticoagulation Effects of Factor Xa Inhibitors) study assessed andexanet alfa's efficacy and safety in patients with a DOAC-associated acute major bleed.[43] Patients had to present with an acute major bleed within 18 hours of receiving rivaroxaban, apixaban, or edoxaban at any dose, or enoxaparin of at least 1 mg/kg per day. Acute major bleeds were defined as potentially life threatening with signs

Table 4. Andexanet Alfa Dosing[37]

Factor Xa Inhibitor	Last Dose	< 8 Hours or Unknown	≥ 8 Hours
Rivaroxaban	≤ 10 mg	Low dose	Low dose
Rivaroxaban	> 10 mg or unknown	High dose	
Apixaban	≤ 5 mg	Low dose	
Apixaban	> 5 mg or unknown	High dose	

Low dose = 400 mg at a target rate of 30 mg/minute followed by 4 mg/minute for ≤ 120 minutes
High dose = 800 mg at a target rate of 30 mg/minute followed by 8 mg/minute for ≤ 120 minutes

or symptoms of hemodynamic compromise bleeding associated with a decrease in hemoglobin level of at least 2 g/dL (or a hemoglobin level of 8 g/dL or lower if no baseline hemoglobin level was available), or bleeding in a critical area or organ. Patients received a bolus dose of 400 mg over 15 minutes followed by the infusion of 480 mg if they had received apixaban and in those who had received rivaroxaban more than seven hours prior to bolus administration. Patients received a bolus dose of 800 mg over a period of 30 minutes and an infusion dose of 960 mg.[43] A total of 352 patients were included in the study, with 64% of patients presenting with ICH and 26% presenting with GI bleed. The median anti-factor Xa activity decreased from 211.8 ng/mL to 14.2 ng/mL and from 149.7 ng/mL to 11.1 ng/mL in patients who had previously received rivaroxaban and apixaban, respectively. Excellent or good hemostasis was achieved in 82% (204/249) of patients at 12 hours. Thrombotic events occurred in 34 (10%) patients including myocardial infarction (7), ischemic stroke (14), DVT (13), and PE (5).[43] Death from cardiovascular causes also occurred in 35 patients within 30 days.

Andexanet alpha's labeling contains a boxed warning for its association with life-threatening adverse events, including arterial and venous thromboembolic events, ischemic events (including myocardial infarction and ischemic stroke), cardiac arrest, and sudden death.[37] It is important to monitor for thromboembolic events and reinitiate anticoagulation as soon as medically appropriate.

Andexanet alfa is supplied in cartons of four single-use vials containing 100 mg each, which after reconstitution with sterile water, contains 10 mg/mL of reversal agent. Reconstituted vials and IV bags are stable at room temperature for eight hours but can be refrigerated (2°C-8°) for up to 24 and 16 hours, respectively.[37] **Table 4** lists andexanet alfa's dosing based on the DOAC used, its dose, and the time since the time since the patient's last dose.

Andexanet alfa was originally distributed with limited quantities available under the Early Supply Program. However, the FDA has since approved new manufacturing processes to allow an upscale of production of the drug to increase access.[45] Andexanet alfa is now available nationwide and facilities with the medication can be located on the drug's website (https://www.andexxa.com/).

Ciraparantag

Ciraparantag, an investigational reversal agent, is a small, synthetic, water-soluble, cationic molecule designed to be a broad-spectrum reversal agent for factor Xa inhibitors, direct thrombin inhibitors, unfractionated heparin, and low-molecular-weight heparin.[46] It achieves anticoagulation reversal through noncovalent hydrogen bonding and charge-charge interactions. In a phase 1 double-blind, placebo-controlled study, researchers used a single dose of ciraparantag (100 to 300 mg) given three hours after a 60 mg oral dose of edoxaban to reverse the anticoagulant effect in healthy volunteers.[43] Edoxaban's anticoagulant effect of was measured by whole-blood clotting time. Ciraparantag returned whole-blood clotting time to within 10% of baseline to restore hemostasis in 10 minutes or fewer. Patients who received placebo achieved baseline hemostasis in 12 to 15 hours. Baseline hemostasis was maintained for 24 hours after ciraparantag administration. Additionally, there was no evidence of procoagulant activity (see **Sidebar**, page 10) after ciraparantag administration and only mild adverse effects were reported (transient mild perioral and facial flushing and dysgeusia [taste disturbances], and moderate headache).[46]

DOAC-Associated Bleeding: Applying Guidelines

The American College of Cardiology (ACC) developed an Expert Consensus Decision Pathway on Management of Bleeding in Patients on Oral Anticoagulants that addresses strategies to manage patients who experience bleeding events on DOACs.[48] Although it developed and published this decision pathway prior to FDA approval of andexanet alfa, the ACC has published updated guidance for anticoagulation reversal which includes andexanet alfa dosing.[49] These documents help guide decision making regarding preventing and managing bleeding, reversing DOACs, and if and when to restart anticoagulation therapy in patients.

Defining and identifying bleeding severity is the key determinant in managing DOAC-associated bleeding. Major bleeding is defined as having one or more of the following factors[48]:

- bleeding in a critical site,
- hemodynamic instability, or
- overt bleeding with a hemoglobin drop ≥2 g/dL or administration of two or more units of packed red blood cells (RBCs).

Bleeding sites that are considered critical are those that compromise the organ's function. ICH and other central nervous system bleeds (intraocular, spinal) and thoracic, intra-abdominal, retroperitoneal, intraarticular, and intramuscular bleeds are all consider critical site bleeds. GI bleeds are not necessarily considered critical site bleeds, but may cause hemodynamic instability depending on the severity.[48]

Hemodynamic instability can be assessed by monitoring factors associated with significant drops in blood pressure. Increased heart rate, systolic blood pressure (SBP) <90 mm Hg, a decrease in SBP >40 mm Hg, or orthostatic blood pressure changes (SBP drop ≥20 mm Hg or diastolic blood pressure drop ≥10 mm Hg upon standing) can indicate hemodynamic instability. However, noninvasive blood pressure measurements are not completely reliable. The pathway recommends obtaining mean arterial pressure (MAP) via invasive measures. A MAP of less than 65 mm Hg serves as the cutoff for hemodynamic instability.[48] Additionally, it is important to monitor patients for surrogate markers of end organ perfusion such as urine output and laboratory markers of renal or hepatic damage.

Patients who experience bleeding associated with drops in hemoglobin of 2 g/dL or more or who require two units of packed RBCs or more are at significantly increased risk of mortality.[48] This is especially true for patients with cardiovascular disease (history of angina, myocardial infarction, heart failure, or peripheral artery disease).[48] If a patient does not meet any of the criteria for a major bleed, the bleed is classified as a nonmajor bleeding event.

Assessing coagulation assays (which measure anticoagulation activity) may be another useful tool. Although routine laboratory monitoring of DOACs is unnecessary for usual patient follow-up, DOACs' effects on these tests may offer valuable insight about potential overexposure and patients at risk of bleeding. However, results of commonly used tests can vary depending on the DOAC (direct thrombin inhibition or direct factor Xa inhibition) and response of the specific reagent used.[48,50,51] Most common coagulation tests yield qualitative results, meaning they simply report whether or not the drug is present. Prothrombin time (PT), activated partial thromboplastin time (aPTT), and thrombin time (TT) can be used in this manner, but results need to be interpreted with caution.[48,50,51] For example, PT and aPTT may be useful for qualitative assessment of rivaroxaban and edoxaban. Prolonged PT and aPTT levels indicate therapeutic or supratherapeutic levels of these DOACs, but normal or low PT or aPTT values do not necessarily mean low levels or absence of these drugs. PT and aPTT are insensitive to apixaban and low or normal values cannot rule out the possibility that clinically relevant apixaban levels are present.

Laboratory tests that provide quantitative data (meaning they reflect the amount of drug ingested or present) specific to DOACs are being used, but the ability to perform these test varies greatly by center and laboratory capabilities. dTT calibrated to dabigatran and ECT can be used to quantitatively assess dabigatran concentrations.[48,50,51] Likewise the chromogenic anti-Xa assay can be calibrated to be DOAC-specific and offer quantitative results,[48,50,51] but these calibrated tests are not widely available or used at this time.

Tech Talk: Procoagulant Activity

When reversing the action of anticoagulant medications, an important consideration is putting patients who are already at-risk for blood clots in further danger of thromboembolic events. Medications may interact by not only reversing the anticoagulant effects, but also by potentially pushing the coagulation cascade in favor of clotting (procoagulant activity). Clotting factors and blood products are nonspecific agents used to reverse and control bleeding. These concentrated factors contain various amounts of clotting factors or blood components such as platelets involved in the clotting cascade.

- Proteins C and S are the body's natural anticoagulants.
- Vitamin K antagonists interfere with protein C and S production which temporarily shifts the clotting cascade in favor of procoagulant activity.

These examples highlight the importance of closely examining the effects of new drugs that may interfere with the clotting cascade either directly or indirectly. The discovery that ciraparantag did not show evidence of procoagulant activity is important regarding the safety of the broad-spectrum investigational reversal product.

Table 5. Laboratory Measurement of DOACs [48,50,51]

Drug	Qualitative Data	Quantitative Data
Dabigatran	TT, aPTT*	Dilute TT ECT ECA
Rivaroxaban, Apixaban, Edoxaban	PT, aPTT†	Chromogenic Anti-Xa‡

aPTT=activated partial thromboplastin time; ECA=ecarin chromogenic assay; ECT=ecarin clotting time; PT=prothrombin time; TT=thrombin time

*Normal TT excludes clinically relevant levels; Prolonged TT does not discriminate between clinically important and insignificant levels; Normal aPTT usually excludes clinically relevant levels; Prolonged aPTT suggests on-therapy or supratherapeutic drug levels
†Normal PT and apt do not exclude clinical relevant levels; Prolonged PT suggests on-therapy or supratherapeutic drug levels
‡Useful for quantification of plasma drug levels only when calibrated with the specific drug of interest

When nonmajor bleeding occurs, reversal of DOACs is not recommended.[48] If a patient experiences a nonmajor bleed, clinicians should employ local measures to control the bleeding and consider discontinuing the DOAC. The decision of whether to hold the DOAC depends on patient specific characteristics, the nature of the bleed, and the risk/benefits of temporarily discontinuing anticoagulation. According to the ACC consensus document, anticoagulation should be held in nonmajor bleeding in the following situations:

- Supratherapeutic anticoagulation
- Invasive procedure needed soon
- Change in the patient's underlying bleeding risk (e.g., new medications, acute deterioration in renal or hepatic function)
- Continued diagnostic evaluation for the site or clinical impact of bleeding warranted
- Baseline severe anemia requiring transfusion of one or more units of packed RBCs
- Relevant medical comorbidities, frailty, or other medical issues requiring observation and treatment
- Concern for slow bleed from a critical site requiring repeat imaging (e.g., head trauma concerning for subdural hematoma)

If none of these or similar situations exist, and the patient does not require hospitalization, a procedure, or transfusion, the pathway recommends not stopping (that is, continuing) anticoagulation.

In managing major bleeding events, the pathway recommends holding all anticoagulants and antiplatelet medications and using reversal. While reversing the DOAC, the treatment team should employ local hemostatic (e.g., pressure, packing) and resuscitation measures simultaneously, if necessary, without delay. The treatment team should use aggressive volume resuscitation such as intravenous isotonic crystalloids (0.9% NaCl or Ringer's lacate), especially in the setting of hemodynamic instability. Supportive measures should also include blood product transfusion when appropriate. Patients with symptomatic anemia or active bleeding should receive RBC transfusions to maintain hemoglobin at 7 g/dL or higher and 8 g/dL or higher in those with coronary artery disease. Platelets and cryoprecipitate are also recommended to maintain a platelet count of at least 50 x 10^9/L and fibrinogen of 100 mg/dL or more respectively.[48]

For DOAC reversal, the treatment team needs to use specific antidotes for dabigatran, rivaroxaban, and apixaban. For dabigatran, idarucizumab 5 g should be administered intravenously. If idarucizumab is unavailable, the guideline recommends administering 4F-PCC or aPCC intravenously at 50 units/kg. For apixaban and rivaroxaban, the guidance recommends administering andexanet alfa according to recommended doses determined by drug and timing of last known dose (**Table 5**). If andexanet alfa is unavailable, it recommends administering 4F-PCC or aPCC 50 units/kg intravenously. Since andexanet alfa is not currently FDA-approved for edoxaban reversal, 4F-PCC IV at 50 units/kg is recommended as first-line and aPCC IV units/kg recommended if 4F-PCC is unavailable. The ACC currently has no recommended strategies for betrixaban reversal, but some institutional guidelines recommend the same reversal strategy as edoxaban. For each of the DOACs, the treatment team can use activated charcoal if the patient ingested the oral anticoagulant within the previous two to four hours.[48,49]

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Once bleeding is controlled and the patient stabilizes, the treatment team's next consideration is whether to restart anticoagulation and the timing if restarting anticoagulation is indicated. In most cases the underlying reason for anticoagulation therapy will warrant restarting anticoagulation. Restarting anticoagulation therapy may not be indicated in the following situations[48]:

- Paroxysmal atrial fibrillation with CHA_2DS_2-VASc score of 1 or above
- Temporary indication (e.g., postsurgical prophylaxis, anticoagulation after an anterior myocardial infarction without left ventricular thrombus, first time provoked VTE fewer than three months ago, or bioprosthetic valve replacement fewer than three months ago)

If a patient has an ongoing indication for anticoagulation however, timing becomes important. A delayed restart is recommended when the bleed occurred in a critical site, the patient has a high risk of re-bleeding or death from a re-bleed, the treatment team cannot identify the source of the bleed, or the patient will need a future surgical intervention. For patients with gastrointestinal bleeds, restarting a DOAC after seven or more days is associated with better outcomes. For patients with ICH, the treatment team should consider delaying oral anticoagulation for approximately four weeks.[48]

Conclusion

DOACs have been proven to be at least as effective as vitamin K antagonists in treating and preventing thrombobemolic events with improvements in safety regarding bleeding. Despite DOAC's improved benefit/risk profile, patients are at increased risk of bleeding as with all anticoagulants. Until relatively recently, dabigatran was the only DOAC with an FDA-approved reversal agent. The approval of andexanet alfa has provided a specific reversal agent for rivaroxaban and apixaban, but these reversal agents are not always widely available. Edoxaban and betrixaban are still without specific reversal agents. This highlights the importance of practitioners familiarizing themselves with DOAC reversal. Pharmacists need to identify patients at elevated risk of bleeding events; assess and categorizie bleeding events when they occur; and know all available treatment options when bleeding events are major or life-threatening.

With the number of patients being initiated on DOAC therapy on the rise, more reversal products in the pipeline, and a paucity of data on some of the current treatment and reversal strategies for DOAC-associated bleeding, this is an evolving topic which should be closely researched and followed.

Figure 2. Advancing Pharmacists and Pharmacy Technicians Role in DOAC-Associated Bleeding

Best

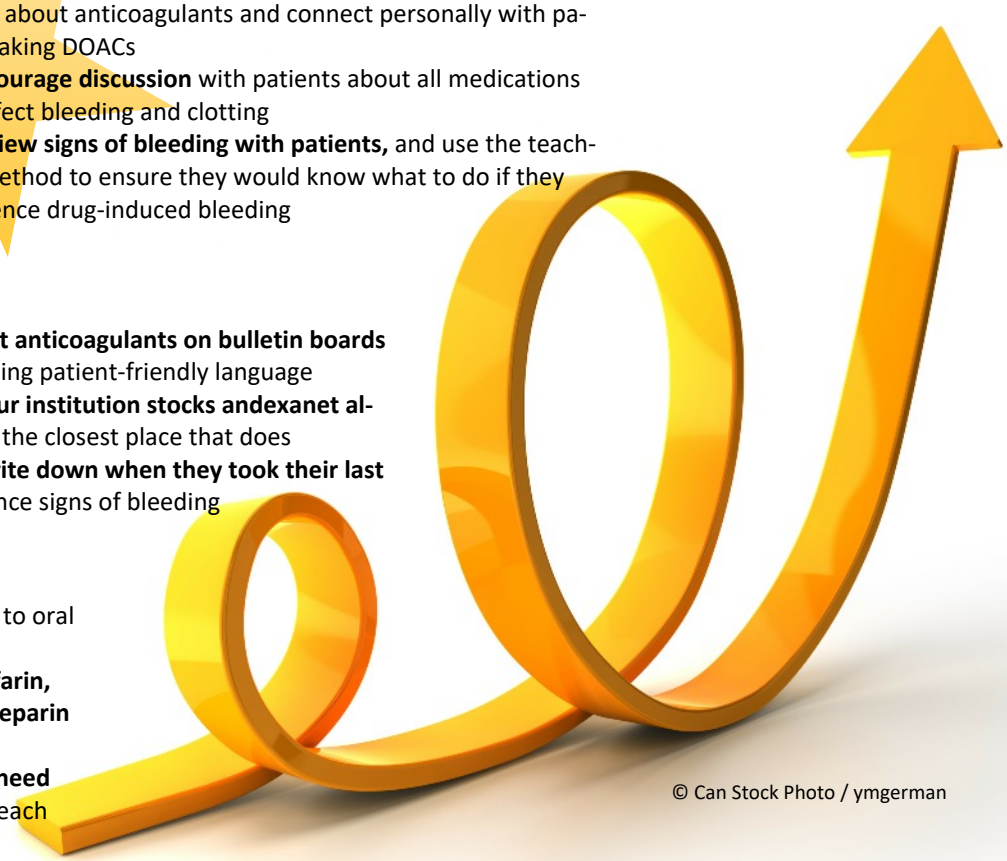
1. **Be COMMUNITY CHAMPIONS.** Track news and FDA information about anticoagulants and connect personally with patients taking DOACs
2. **Encourage discussion** with patients about all medications that affect bleeding and clotting
3. **Review signs of bleeding with patients,** and use the teach-back method to ensure they would know what to do if they experience drug-induced bleeding

Better

1. **Post information about anticoagulants on bulletin boards in patient waiting areas** using patient-friendly language
2. **Determine whether your institution stocks andexanet alpha and idarucizumab**, or the closest place that does
3. **Educate patients to write down when they took their last DOAC dose** if they experience signs of bleeding and seek care

Good

1. **Be certain to apply auxillary labels** to oral anticoagulant vials
2. **Know how DOACs differ from warfarin, low molecular weight heparins, and heparin** and why bleeding is a risk
3. **Understand why so many people need anticoagulants** and be able to explain each condition



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