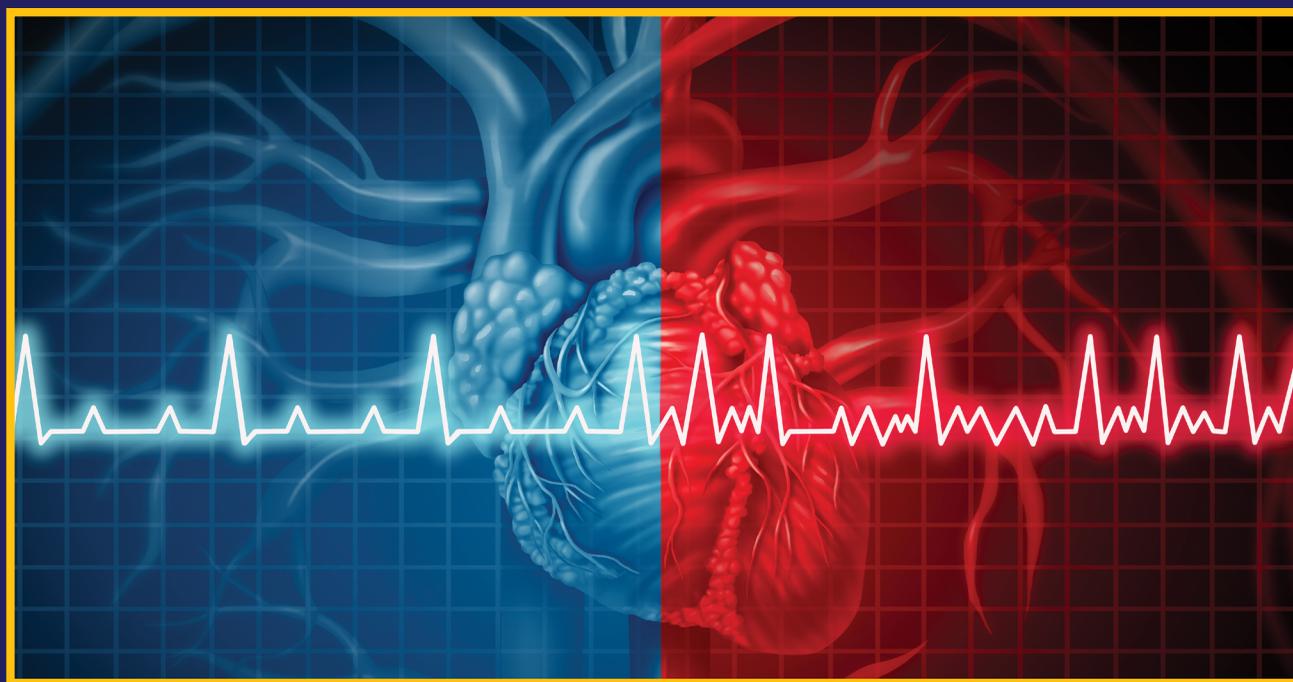
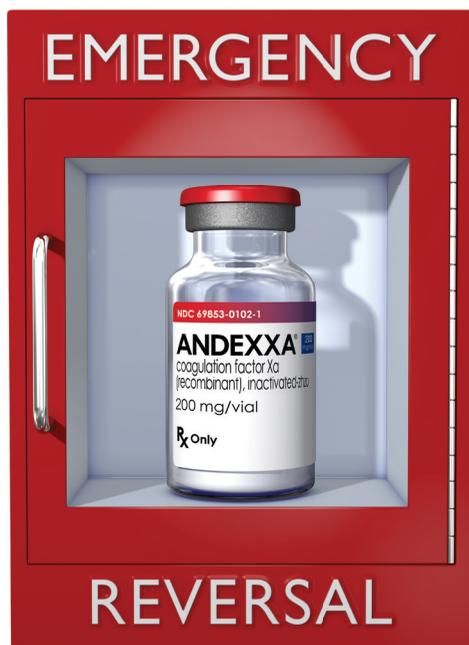


# MEETING THE CHALLENGES OF DIRECT-ACTING ORAL ANTICOAGULANT USAGE IN FEDERAL MEDICINE



# Now Covered on VA National Formulary



When treating life-threatening or uncontrolled bleeds in patients on apixaban or rivaroxaban

## REACH FOR ANDEXXA®

(coagulation factor Xa (recombinant), inactivated-zhzo)

### The Only FDA-approved Specific Reversal Agent<sup>1</sup>

#### INDICATION

ANDEXXA (coagulation factor Xa (recombinant), inactivated-zhzo) is a recombinant modified human factor Xa (FXa) protein indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

This indication is approved under accelerated approval based on the change from baseline in anti-FXa activity in healthy volunteers. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies that demonstrate an improvement in hemostasis in patients.

#### Limitations of Use

ANDEXXA has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban or rivaroxaban.

Please see additional Important Safety Information on adjacent page and Brief Summary of full Prescribing Information including Boxed Warning on following page.

For further information, please visit [ANDEXXA.com](http://ANDEXXA.com)

#### SELECT IMPORTANT SAFETY INFORMATION

##### **WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATHS**

*See full prescribing information for complete boxed warning*

**Treatment with ANDEXXA has been associated with serious and life-threatening adverse events, including:**

- Arterial and venous thromboembolic events
- Ischemic events, including myocardial infarction and ischemic stroke
- Cardiac arrest
- Sudden deaths

**Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.**

#### WARNINGS AND PRECAUTIONS

##### **Thromboembolic and Ischemic Risks**

The thromboembolic and ischemic risks were assessed in 185 patients who received the Generation 1 product and in 124 patients who received the Generation 2 product. The median time to first event was six days, and patients were observed for these events for 30 days following the ANDEXXA infusion. Of the 86 patients who received Generation 1 product and were re-anticoagulated prior to a thrombotic event, 11 (12.7%) patients experienced a thromboembolic, ischemic event, cardiac event or death.



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## Rapid reversal of anti-FXa activity within 2 minutes

following bolus administration in older, healthy volunteers on apixaban or rivaroxaban.<sup>1\*</sup>

\*ANNEXA-A and ANNEXA-R were two Phase 3 studies designed to establish the efficacy and safety of ANDEXXA for the reversal of anticoagulation with apixaban or rivaroxaban in older healthy volunteers. The primary endpoint of both studies was mean percent change in anti-FXa activity.<sup>1,2</sup>



**Expert guidance** recommends Andexxa for first-line therapy to reverse apixaban or rivaroxaban in patients with life-threatening or uncontrolled bleeds.<sup>3</sup>

### SELECT IMPORTANT SAFETY INFORMATION

#### Thromboembolic and Ischemic Risks (continued)

Monitor patients treated with ANDEXXA for signs and symptoms of arterial and venous thromboembolic events, ischemic events, and cardiac arrest. To reduce thromboembolic risk, resume anticoagulant therapy as soon as medically appropriate following treatment with ANDEXXA.

The safety of ANDEXXA has not been evaluated in patients who experienced thromboembolic events or disseminated intravascular coagulation within two weeks prior to the life-threatening bleeding event requiring treatment with ANDEXXA. Safety of ANDEXXA also has not been evaluated in patients who received prothrombin complex concentrates, recombinant factor VIIa, or whole blood products within seven days prior to the bleeding event.

#### Re-elevation or Incomplete Reversal of Anti-FXa Activity

The time course of anti-FXa activity following ANDEXXA administration was consistent among the healthy volunteer studies and the ANNEXA-4 study in bleeding patients. Compared to baseline, there was a rapid and substantial decrease in anti-FXa activity corresponding to the ANDEXXA bolus. This decrease was sustained through the end of the ANDEXXA continuous infusion. The anti-FXa activity returned to the placebo levels approximately two hours after completion of a bolus or continuous infusion. Subsequently, the anti-FXa activity decreased at a rate similar to the clearance of the FXa inhibitors.

Thirty-eight patients who received the Generation 1 product were anticoagulated with apixaban and had baseline levels of anti-FXa activity >150 ng/mL. Nineteen of these 38 (50%) patients experienced a > 93% decrease from baseline anti-FXa activity after administration of ANDEXXA. Eleven patients who were anticoagulated with rivaroxaban had baseline anti-FXa activity levels > 300 ng/mL. Five of the 11 patients experienced a > 90% decrease from baseline anti-FXa activity after administration of ANDEXXA. Anti-FXa activity levels for patients who received the Generation 2 product were not available.

#### Adverse Reactions

The most common adverse reactions ( $\geq 5\%$ ) in patients receiving ANDEXXA were urinary tract infections and pneumonia.

The most common adverse reactions ( $\geq 3\%$ ) in healthy volunteers treated with ANDEXXA were infusion-related reactions.

#### Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. Using an electrochemiluminescence (ECL)-based assay, 145 Generation 1 ANDEXXA-treated healthy subjects were tested for antibodies to ANDEXXA as well as antibodies cross-reacting with Factor X (FX) and FXa. Low titers of anti-ANDEXXA antibodies were observed in 26/145 healthy subjects (17%); 6% (9/145) were first observed at Day 30 with 20 subjects (14%) still having titers at the last time point (Days 44 to 48). To date, the pattern of antibody response in patients in the ongoing ANNEXA-4 study who received the Generation 1 product has been similar to that observed in healthy volunteers with 6% (6/98) of the patients having antibodies against ANDEXXA. None of these anti-ANDEXXA antibodies were neutralizing. No antibodies cross-reacting with FX or FXa were detected in healthy subjects (0/145) or in bleeding patients (0/98) to date. There is insufficient data to assess for the presence of anti-ANDEXXA antibodies for subjects who received the Generation 2 product.

To report SUSPECTED ADVERSE REACTIONS, contact Portola Pharmaceuticals, Inc. at 1-866-777-5947 or the FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

**References:** 1. ANDEXXA [prescribing information]. South San Francisco, CA: Portola Pharmaceuticals Inc.; 2019. 2. Siegal DM et al. *N Engl J Med*. 2015;373(25):2413-2424. 3. ManageAnticoag: Quick Reference—Guidance for Administering Reversal Agents. American College of Cardiology website. [http://tools.acc.org/ManageAnticoag/?\\_ga=2.55615467.1199444917.1566403095-1809208985.1566403095#/content/quick-reference/](http://tools.acc.org/ManageAnticoag/?_ga=2.55615467.1199444917.1566403095-1809208985.1566403095#/content/quick-reference/). Accessed September 18, 2019.

Please see additional Important Safety Information on adjacent page and Brief Summary of full Prescribing Information including Boxed Warning on following page.

**Andexxa**<sup>®</sup>  
Coagulation Factor Xa  
(Recombinant), Inactivated-zhzo

**ANDEXXA**® (coagulation factor Xa (recombinant), inactivated-zhzo)  
Lyophilized Powder for Solution For Intravenous Injection  
Rx Only

**BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION.**

This does not include all the information needed to use ANDEXXA® safely and effectively. See full Prescribing Information for ANDEXXA®.

**WARNING: THROMBOEMBOLIC RISKS, ISCHEMIC RISKS, CARDIAC ARREST, AND SUDDEN DEATHS**

See full prescribing information for complete boxed warning

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- Ischemic events, including myocardial infarction and ischemic stroke
- Cardiac arrest
- Sudden deaths

Monitor for thromboembolic events and initiate anticoagulation when medically appropriate. Monitor for symptoms and signs that precede cardiac arrest and provide treatment as needed.

**INDICATIONS AND USAGE**

ANDEXXA is indicated for patients treated with rivaroxaban or apixaban, when reversal of anticoagulation is needed due to life-threatening or uncontrolled bleeding.

This indication is approved under accelerated approval based on the change from baseline in anti-FXa activity in healthy volunteers. An improvement in hemostasis has not been established. Continued approval for this indication may be contingent upon the results of studies to demonstrate an improvement in hemostasis in patients.

Limitation of Use

ANDEXXA has not been shown to be effective for, and is not indicated for, the treatment of bleeding related to any FXa inhibitors other than apixaban or rivaroxaban.

**CONTRAINDICATIONS**

None.

**WARNINGS AND PRECAUTIONS**

**Thromboembolic and Ischemic Risks**

The thromboembolic and ischemic risks were assessed in 185 patients who received the Generation 1 product and in 124 patients who received the Generation 2 product. The median time to first event was six days, and patients were observed for these events for 30 days following the ANDEXXA infusion. Of the 86 patients who received Generation 1 product and were re-anticoagulated prior to a thrombotic event, 11 (12.7%) patients experienced a thromboembolic, ischemic event, cardiac event or death.

Monitor patients treated with ANDEXXA for signs and symptoms of arterial and venous thromboembolic events, ischemic events, and cardiac arrest. To reduce thromboembolic risk, resume anticoagulant therapy as soon as medically appropriate following treatment with ANDEXXA.

The safety of ANDEXXA has not been evaluated in patients who experienced thromboembolic events or disseminated intravascular coagulation within two weeks prior to the life-threatening bleeding event requiring treatment with ANDEXXA. Safety of ANDEXXA also has not been evaluated in patients who received prothrombin complex concentrates, recombinant factor VIIa, or whole blood products within seven days prior to the bleeding event.

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**ADVERSE REACTIONS**

The most common adverse reactions (≥ 5%) in patients receiving ANDEXXA were urinary tract infections and pneumonia.

The most common adverse reactions (≥ 3%) in healthy volunteers treated with ANDEXXA were infusion-related reactions.

**Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In the pooled safety analysis of clinical trials of ANDEXXA, 223 healthy volunteers received FXa inhibitors followed by treatment with ANDEXXA. The frequency of adverse reactions was similar in the ANDEXXA-treated group (120/223, 54%) and the placebo-treated group (54/94, 57%). Infusion-related adverse reactions occurred in 18% (39/223) of the ANDEXXA-treated group, and was the only adverse reaction that occurred more frequently than in the placebo group. No serious or severe adverse reactions were reported.

The ANNEXA-4 study is an ongoing multinational, prospective, open-label study using ANDEXXA in patients presenting with acute major bleeding and who have recently received an FXa inhibitor. To date, safety data are available for 185 patients who received the Generation 1 product and for

124 subjects who received the Generation 2 product. Fifty-nine percent of the 185 patients who received the Generation 1 product and 69% of the 124 patients who received the Generation 2 product were older than 75 years. Patients had received either apixaban (98/185; 53%) or rivaroxaban (72/185; 40%) as anticoagulation treatment for atrial fibrillation (143/185; 77%) or venous thromboembolism (48/185; 26%). In the majority of patients, ANDEXXA was used to reverse anticoagulant therapy following either an intracranial hemorrhage (106; 57%) or a gastrointestinal bleed (58; 31%), with the remaining 21 patients (11%) experiencing bleeding at other sites. Patients were assessed at a Day 30 follow-up visit following infusion of ANDEXXA.

Deaths

In the ongoing ANNEXA-4 study, there were 25 deaths (14%) amongst the 185 patients receiving the Generation 1 product. These deaths occurred prior to the Day 30 follow-up visit. Eight patients died within ten days after the ANDEXXA infusion. The percentage of patients, by bleeding type, who died prior to the Day 30 follow-up visit was: 14% for intracranial bleeding, 10% for gastrointestinal bleeding, and 19% for other bleeding types. There were 23 deaths (18%) amongst the 124 patients who received Generation 2 that occurred prior to the Day 30 follow-up visit.

Thromboembolic Events

In the ongoing ANNEXA-4 study, 33/185 (17.8%) patients receiving the Generation 1 product experienced one or more of the following overall thromboembolic events: deep venous thrombosis (11/33; 33%), ischemic stroke (9/33; 24%), acute myocardial infarction (5/33; 15%), pulmonary embolism (5/33; 15%), cardiogenic shock (3/33; 9%), sudden death (2/33; 6%), congestive heart failure (2/33; 6%), acute respiratory failure (2/33; 6%), cardiac arrest (1/33; 3%), cardiac thrombus (1/33; 3%), embolic stroke (1/33; 3%), iliac artery thrombosis (1/33; 3%), and non-sustained ventricular tachycardia (1/33; 3%). The median time to the first event in these 33 subjects was six days. Eleven of 33 (33%) patients were on antithrombotic therapy at the time of the event. Patients who received the Generation 2 product experienced a similar rate of overall thromboembolic events (17.7%) as the Generation 1 product.

No thromboembolic events were observed in 223 healthy volunteers who received FXa inhibitors and were treated with ANDEXXA.

Infusion-related Reactions

Infusion-related reactions occurred in 18% (39/223) of ANDEXXA-treated healthy volunteers vs. 6% (6/94) of placebo-treated subjects. These reactions were characterized by a range of symptoms including flushing, feeling hot, cough, dysgeusia, and dyspnea. Symptoms were mild to moderate in severity, and 90% (35/39) did not require treatment. One subject with a history of hives prematurely discontinued ANDEXXA after developing mild hives.

**Immunogenicity**

As with all therapeutic proteins, there is the potential for immunogenicity. Using an electrochemiluminescence (ECL)-based assay, 145 Generation 1 ANDEXXA-treated healthy subjects were tested for antibodies to ANDEXXA as well as antibodies cross-reacting with Factor X (FX) and FXa. Low titers of anti-ANDEXXA antibodies were observed in 26/145 healthy subjects (17%); 6% (9/145) were first observed at Day 30 with 20 subjects (14%) still having titers at the last time point (Days 44 to 48). To date, the pattern of antibody response in patients in the ongoing ANNEXA-4 study who received the Generation 1 product has been similar to that observed in healthy volunteers with 6% (6/98) of the patients having antibodies against ANDEXXA. None of these anti-ANDEXXA antibodies were neutralizing. No antibodies cross-reacting with FX or FXa were detected in healthy subjects (0/145) or in bleeding patients (0/98) to date. There is insufficient data to assess for the presence of anti-ANDEXXA antibodies for subjects received the Generation 2 product.

Detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to ANDEXXA with the incidence of antibodies to other products may be misleading.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Risk Summary

There are no adequate and well-controlled studies of ANDEXXA in pregnant women to inform patients of associated risks. Animal reproductive and development studies have not been conducted with ANDEXXA.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Labor or Delivery

The safety and effectiveness of ANDEXXA during labor and delivery have not been evaluated.

**Lactation**

Risk Summary

There is no information regarding the presence of ANDEXXA in human milk, the effects on the breastfed child, or the effects on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ANDEXXA and any potential adverse effects on the breastfed child from ANDEXXA or from the underlying maternal condition.

**Pediatric Use**

The safety and efficacy of ANDEXXA in the pediatric population have not been studied.

**Geriatric Use**

Of the 185 patients who received the Generation 1 product in the ANNEXA-4 study of ANDEXXA, 161 were 65 years of age or older, and 113 were 75 years of age or older. Of the 124 subjects who received the Generation 2 product, 92 subjects were 75 years of age or older. No overall differences in safety or efficacy were observed between these subjects and younger patients, and other reported clinical experience has not identified differences in responses between elderly and younger patients; however, greater sensitivity of some older individuals cannot be ruled out.

The pharmacokinetics of ANDEXXA in older (> 65 years; n=10) patients were not different compared to younger (18-45 years; n=10) patients.

Portola Pharmaceuticals, Inc.



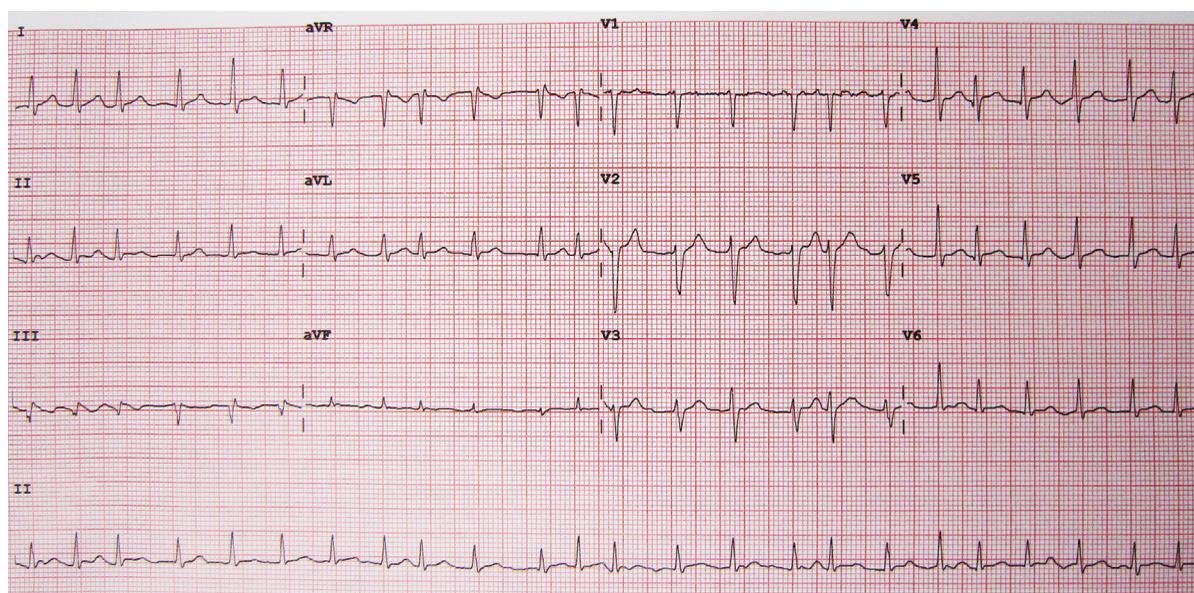
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January 2019

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Art and production by CranCentral Graphics.

Image above: A 12-lead ECG showing atrial fibrillation at approximately 150 beats per minute. —Source: Wikipedia, James Heilman, MD

# SAFER, SIMPLER, REVERSIBLE: DOACs RESHAPE VA ANTICOAGULATION THERAPY ACROSS SYSTEM

PALO ALTO, CA—Ten years ago choosing an anticoagulation therapy boiled down to warfarin or—warfarin. Today, physicians and patients in the VA and elsewhere have more anticoagulant choices than ever, and those newer options have largely displaced warfarin for many indications.

In 2010, the U.S. Food and Drug Administration approved the first direct oral anticoagulant, dabigatran etexilate mesylate, an oral direct thrombin inhibitor. Rivaroxaban gained approval in 2011, followed by apixaban in 2012, edoxaban in 2015, and betrixaban in 2017.

All four of the “xabans” are oral, selective factor Xa inhibitors. Warfarin is a vitamin K antagonist that inhibits the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X as well as two anticoagulant proteins.

“Across almost every healthcare system and payer, including the VA, DOACs have seen a tidal rise of use,” said Minang Turakhia, MD, MAS, director of cardiac electrophysiology at the VA Palo Alto, CA, Health Care System and executive director of the Center for Digital Health at Stanford University.

Between 2013 and 2014, the use of DOACs, originally called “novel oral anticoagulants, nationwide and within the VA and DoD tripled. By

late 2016, the new drugs accounted for two-thirds of all new prescriptions for anticoagulants and nearly half of all anticoagulant prescriptions overall at the VA.<sup>1</sup>

Today, about 217,000 veterans take a DOAC and 86,000 are on warfarin, according to Heather L. Worth, PharmD, national program manager for Clinical Pharmacy Practice Program and Outcomes Assessment, VA Pharmacy Benefits Management. “That’s double the 2011 number, when 150,000 veterans were on warfarin,” she said.

“The VA has done a great job responding to this change and thought about systemwide implementation and usage early on,” Turakhia told *U.S. Medicine*. Right from the start, the VA adapted existing warfarin clinics to support

DOAC initiation (see Article 3) and offered educational programs and materials for providers about the new drugs.

The most common indications for DOACs are for stroke prevention in patients with atrial fibrillation and for the prevention of venous thromboembolism.

The 2019 American Heart Association/American College of Cardiology/Heart Rhythm Society Guidelines recommend DOACs over warfarin for patients with atrial fibrillation except in those with moderate to severe mitral stenosis or a mechanical heart valve.

## SWITCHING TO DOACs

“Where we are today, if someone comes in for a new indication for atrial fibrillation, we’re more like-

*“Where we are today, if someone comes in for a new indication for atrial fibrillation, we’re more likely to recommend a DOAC unless they’re in a special population.”*



— Minang Turakhia, MD, MAS,  
director of cardiac electrophysiology, VA Palo Alto

ly to recommend a DOAC unless they're in a special population," Turakhia said. Special cases include patients with valvular atrial fibrillation or with mechanical valves, for whom DOACs have not been approved, and some patients with chronic kidney disease.

"What we had not seen until recently is conversion from patients on warfarin to a DOAC."

But that now is changing. "First, patients with not great [international normalization ratio] INR control transitioned, now, even if a patient is well-managed on warfarin, we discuss the potential benefits of switching," he noted.

Several factors have driven the rapid adoption of DOACs. "Major randomized controlled trials showed that DOACs are as good or superior to warfarin in stroke prevention in patients with atrial fibrillation and intracranial hemorrhage is lower with DOACs, while time in therapeutic range is higher," Turakhia said.

"There are also advantages for patients. They don't need ongoing INR monitoring and dosing adjustments; there's a simple dosing strategy and they are more convenient," he added. Unlike warfarin, the DOACs have few interactions with other drugs or food.

No head-to-head trials have directly compared the DOACs to each other, so choosing between them varies by facility, physician preference, indication and patient characteristics.

While the drugs have many similarities, administration differs in important ways between them.

"With dabigatran, you have to have a certain amount injected

first, and most people prefer not having to use injection. Some of the others can be used as monotherapy, without an injection," said Tracy Minichiello, MD, chief of the anticoagulation and thrombosis services in the division of hematology at the San Francisco VAMC and clinical professor medicine at the University of California San Francisco. "For atrial fibrillation, rivaroxaban can be dosed once a day, which may be best for patients with compliance issues."

## NATIONAL CRITERIA

The VA's Pharmacy Benefit Management team "has done an exceptional job creating national criteria for use," that guide physicians' choice in specific situations, Turakhia said.

The VA's drug class review summarizes the clinical trials supporting each indication for the drugs and the results for special populations, including pregnant or nursing patients and the very old, and discusses drug interactions. The guidance also notes which drugs can be put in pillboxes and which have to stay in original packaging as well as whether the drugs can be crushed, mixed with food or administered via feeding tubes.

"VA has been really proactive with anticoagulant use and guidance to help clinicians. It's done a great job of providing evidence or expert-based guidance," Minichiello said in an interview with *U.S. Medicine*.

The support is particularly valuable when trying to achieve the delicate balance needed for many patients who require a blood thinner. "Anticoagulation is a risky

business. These are great, incredibly effective medications, but they have risk," she added.

The DOACs have a lower rate of major bleeds than warfarin, but some patients and physicians have been particularly concerned about the risk of bleeds in the absence of a specific reversal agent for the drugs. The FDA approval of reversal agents for dabigatran in 2015 and factor Xa inhibitors in 2018 may put some of those concerns to rest and increase DOAC use, Minichiello noted. (See article on page 10.)

Other factors could drive down DOAC use over time. Compared to 10 or 20 years ago, "warfarin is better managed; DOACs are better understood; patients have better blood pressure control and physicians are better about prescribing aspirin to only patients who need it," Turakhia explained.

"Anticoagulation may not be the right choice for every patient with atrial fibrillation. They may be getting atrial fibrillation at the end of life," he said. "We have amazing therapies to maintain normal sinus rhythm, so do all patients still need to be on anticoagulants for life? New trials are looking to see if we can have periods when patients don't need anticoagulation when they are not having atrial fibrillation. That's the flip side of undertreating—we may be deimplementing for some patients."

<sup>1</sup> Rose AJ, Goldberg R, McManus DD, Kapoor A, Want V, Liu W, Yu H. Anticoagulant prescribing for non-valvular atrial fibrillation in the Veterans Health Administration. *J Am Heart Assoc*. 2019 Sep 3;8(17):e012646. doi:10.1161/JAHA.119.012646. Epub 2019 Aug 23.

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## DOAC USES RAPIDLY EXPAND WITH NEW INDICATIONS

Dabigatran, apixaban, edoxaban and rivaroxaban all have FDA approval for use to reduce the risk of stroke and blood clots in patients with nonvalvular atrial fibrillation and treatment of deep vein thrombosis and pulmonary embolism. Dabigatran, apixaban and rivaroxaban are also indicated for the prevention of blood clots after hip or knee replacement surgery.

New indications continue to emerge for DOACs.

**Hospitalized patients:** Betrixaban and, as of mid-October, rivaroxaban are also approved for use in the prevention of VTE in hospitalized acutely ill medical patients at risk for thromboembolic complications who are not at high risk of bleeding. Patients can continue on both for several weeks after discharge.

**Cardiovascular events:** Rivaroxaban is the only DOAC to date with an indication to reduce the risk of cardiovascular death, myocardial infarction and stroke in patients with coronary artery disease or peripheral artery disease. For this indication, the DOAC must be taken with aspirin. The FDA based its approval on the COMPASS trial, which enrolled 27,395 patients and terminated early because the rivaroxaban/aspirin combination demonstrated superiority at 23 months.<sup>1</sup>

“The COMPASS trial was groundbreaking. It was one of the most important cardiology trials of the decade and showed so much benefit,” said Turakhia. “For other drugs to receive the same approval, they would have to do the same kind of trial and I don’t think they are. It’s a huge indication that affects many more people in the VA than atrial fibrillation.”

**Dialysis:** The use of DOACs in patients with renal impairment has been a matter of ongoing debate. All DOACs are renally cleared to some extent. Dose reductions are recommended when using dabigatran, edoxaban, and rivaroxaban in patients with moderate renal impairment and they should not be used in patients with severe renal impairment or those on dialysis.

Apixaban can be used in patients with end-stage renal disease and patients on dialysis, at a full or reduced dose, according to its package insert. A recent study raised questions about using the full 5 mg dose in these patients and the two prospective studies done to date have had only 15 patients combined.<sup>2</sup> Two ongoing studies, RENAL-AF and AXADIA, are evaluating the risks and benefits of apixaban and warfarin in these challenging patients.

“So far, the studies are underenrolled,” noted Turakhia. The bigger issue, though, is identifying a real benefit for anticoagulation for patients on dialysis. “They are at risk for so many things, would they live long enough to sustain a benefit from anticoagulation?” he asked.

Recent and ongoing studies have also identified several promising potential indications for DOACs.

**Cancer:** The Phase 3 ADAM trial determined that apixaban was as safe and 80% more effective than dalteparin in reducing the risk of recurrence of venous thromboembolism

associated with cancer.<sup>3</sup> The CASSINI study showed a significant reduction in VTE and death in cancer patients initiating systemic treatment during the on treatment period with rivaroxaban, while the AVERT trial found that apixaban significantly reduced the rate of VTE in intermediate-to-high risk ambulatory cancer patients starting chemotherapy.<sup>4,5</sup>

**LVT:** A small retrospective study indicated that patients with left ventricular thrombi had similar rates of systemic embolism as those on warfarin and a meta-analysis of 30 articles found a thrombus resolution success rate in LVT of 81%, 100% and 88.9% for rivaroxaban, apixaban and dabigatran.<sup>6,7</sup>

**Bleeding following stenting:** The ENTRUST-AF PCI trial recently found edoxaban plus a P2Y12 inhibitor (clopidogrel) as effective as the standard triple therapy of a P2Y12 inhibitor plus aspirin and a vitamin K antagonist in preventing bleeding in patients with atrial fibrillation who have undergone coronary stenting.<sup>8</sup> The results echoed previous trials that determined dual therapy with apixaban, rivaroxaban or dabigatran and a P2Y12 inhibitor reduced bleeding after percutaneous coronary intervention compared to the standard triple therapy with no increase in thromboembolic events.

<sup>1</sup> Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease. *NEJM*. 2017 Oct 5;377:1319-1330.

<sup>2</sup> Mavrakanas TA, Samer CF, Nessim SJ, Frisch G, Lipman ML. Apixaban Pharmacokinetics at Steady State in Hemodialysis Patients. *J Am Soc Nephrol*. 2017 Jul;28(7):2241-2248.

<sup>3</sup> McBane RD, Wysokinski WE, Le-Rademacher J, et al. Apixaban, dalteparin, in active cancer associated venous thromboembolism, the ADAM VTE trial. Abstract #421. Presented at the 2018 ASH Annual Meeting, Dec 2, 2018; San Diego, CA.

<sup>4</sup> Khorana AA, Soff GA, Kakkar AK, et al; CASSINI Investigators. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. *N Engl J Med*. 2019 Feb 21;380(8):720-728. doi:10.1056/NEJMoa1814630.

<sup>5</sup> Carrier M, Abou-Nassar K, Mallick R, et al; AVERT Investigators. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. *N Engl J Med*. 2019 Feb 21;380(8):711-719.

<sup>6</sup> Robinson A, Ruth B, Dent J. Direct oral anticoagulants compared to warfarin for left ventricular thrombi: A single center experience. *JACC*. 2018 Mar;71(11):S735.

<sup>7</sup> Kajj M, Shokr M, Ramappa P. Use of Direct Oral Anticoagulants in the Treatment of Left Ventricular Thrombus: Systematic Review of Current Literature. *Am J Ther*. 2019 Jan 29.

<sup>8</sup> Vranckx P, Valgimigli M, Eckardt L. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomized, open label, Phase 3b trial. *Lancet*. 2019 Oct 12;394(10206):P1335-1343.

Condition	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Betrixaban
<b>Stroke Prevention in Atrial Fibrillation</b>	✓	✓	✓	✓#	
<b>Venous Thromboembolism Treatment (VTE)</b>					
Acute	✓*	✓	✓	✓*	
Extended (>six months)	✓	✓	✓	-	
<b>Deep Vein Thrombosis Prevention following Hip/Knee Arthroplasty</b>	✓	✓	✓		
<b>VTE Prevention in Hospitalized Acutely Ill Patients/extended</b>		✓			✓
<b>Cardiovascular Event Prevention in Coronary or Peripheral Artery Disease**</b>		✓			

# Edoxaban is not recommended for atrial fibrillation patients with excellent renal function (creatinine clearance >95 mL/min) as a subgroup analysis indicated it may be less effective than warfarin in these patients.

\* Edoxaban and dabigatran are approved for the acute treatment of venous thromboembolism only following five to 10 days of treatment with a parenteral anticoagulant such as low molecular weight heparin, fondaparinux or heparin.

\*\* Rivaroxaban is approved in combination with aspirin for reduction of risk of cardiovascular death, myocardial infarction or stroke in patients with PAD or CAD.

# NEGATIVE DIRECT-TO-CONSUMER ADS ABOUT DOAC BLEEDING KEPT VETERANS OFF THE DRUGS

## *Reversal Agents Have Quieted Concerns, Increased Usage*

SAN FRANCISCO—Direct acting oral anticoagulants have a lower risk of major bleeding than warfarin and clinicians have had options for controlling major bleeds for several years. That’s not the message patients have heard, though.

“Patients have been pretty strongly affected by negative direct-to-consumer advertising about bleeding and that’s created a barrier for many veterans who would be good candidates for DOACs,” said Tracy Minichiello, MD, chief of the anticoagulation and thrombosis services in the division of hematology at the San Francisco VAMC and clinical professor of medicine at the University of California San Francisco.

“There were concerns also for physicians. They had a reversal agent for warfarin. It’s comforting knowing that there’s something available in the small chance that you need to reverse” the action of an anticoagulant, she told *U.S. Medicine*.

Now, physicians and patients have specific reversal agents for several DOACs. Idarucizumab, a reversal agent for dabigatran, received U.S. Food and Drug approval in 2015. Derived from humanized monoclonal antibody segments, the drug has a 350 times stronger affinity for dabigatran than dabigatran has

for thrombin, allowing it to rapidly neutralize the anticoagulant without interrupting platelet aggregation by linking with other thrombin-associated factors or proteins.

Andexanet alfa, a novel modified recombinant human factor Xa, gained approval as a reversal agent for apixaban and rivaroxaban in 2018. Studies are evaluating andexanet alfa in the other direct factor Xa inhibitors on the market, edoxaban and betrixaban, as well as for indirect Xa inhibitors such as low molecular weight heparin and fondaparinux.

A third agent, ciraparantag acetate, is in development. A small synthetic water-soluble molecule designed to bind to both direct factor Xa and IIa inhibitors as well as indirect factor Xa inhibitors and unfractionated heparins, ciraparantag has demonstrated effective reversal of edoxaban, LMWH, apixaban and rivaroxaban in small studies of healthy volunteers.

“Availability of reversal agents has made a difference for patients with concerns raised by ‘call us if you’ve had a bleed’ advertisements soliciting patients for legal cases,” Minichiello said. “We’ve literally had patients say, ‘We’re waiting for approval of that medication,’” before they would start on a DOAC.

Access to Idarucizumab may have had some effect already. “People think differently about dabigatran, but I don’t know if there’s been a big swing nationally,” she added. “Other agents have a strong hold for atrial fibrillation in particular as they have a better safety profile for select patients. Having the next reversal agent will have an impact because so many patients are on the anti-Xa agents.”

While andexanet alfa gained approval in May 2018, its distribution was initially limited to 40 hospitals. The FDA permitted broad distribution in January.

Both reversal agents are available in the VA, which has created new national criteria for use for idarucizumab and andexanet alfa to guide individual hospitals. “If you’re standing next to a patient with a life-threatening bleed and know the reversal agent works, it provides more confidence. Guidance provides expert opinion or extrapolation when you don’t the data or randomized clinical trials to help you and you really need to know how to move forward,” Minichiello said.

Before the reversal agents became available, guidelines recommended reversing life-threatening bleeds in patients on factor Xa inhibitors with non-specific prohemostatic agents such as

prothrombin complex concentrate and activated PCC. “We don’t have studies yet comparing andexanet alfa to aPCC or four-factor PCC, so we don’t know whether it is as safe or is associated with more thrombosis,” Minichiello cautioned.

Still, a tested, approved reversal agent is reassuring. “These agents have a much lower bleeding risk and much lower intracranial hemorrhage risk, so we have to worry about bleeds less often than with warfarin, but having a specific reversal agent does provide comfort,” she said.

That increased comfort may translate into greater use of the DOACs. “We—everyone in the country—do still undertreat atrial fibrillation. They fear the bleed more than the clot. I do hope that use increases as these medications have a better safety profile than warfarin,” Minichiello explained.

Greater use could lead to better care, she added. “At the VA, we don’t have the hurdle of price, so I hope we will use DOACs appropriately to reduce risk in more patients,” with concerns about reversal addressed. Prior to the agents coming on the market, “many physicians have chosen to use aspirin, but it is not particularly effective in preventing stroke in patients with atrial fibrillation.”

The AVERROES trial demonstrated apixaban’s superiority to aspirin in reducing the risk of stroke in patients with atrial fibrillation without increasing the risk of bleeding. The ARISTOTLE trial found apixaban was better than warfarin for stroke prevention and

had a lower risk of bleeding and all-cause mortality.<sup>1,2</sup>

Some DOACs still do not have specific reversal agents. “Andexanet alfa received approval for only apixaban and rivaroxaban, but all four anti-Xa anticoagulants work the same way,” Minichiello noted. “The Anticoagulation Forum published reversal guidance suggesting that off label use of andexanet alfa for edoxaban and betrixaban, but that’s just one guideline, not the standard of care or a treatment that’s FDA approved.”

## WHEN TO USE?

DOACs have a much shorter half-life than warfarin’s 35 hours, so clinicians can manage many bleeds with supportive measures. Elimination half-life for the DOACs ranges from about six hours to 17 hours in patients with normal renal function.<sup>3</sup>

In an emergency situation, though, it may be difficult to tell whether a patient is still experiencing an anticoagulation effect from the drugs as conventional coagulation testing lacks the sensitivity and specificity necessary and thresholds have not been established for all DOACs below which an effect could be excluded. Thrombin time, prothrombin time or activated partial thromboplastin time may provide a general estimate of altered hemostasis when time is of the essence.<sup>4</sup>

The Anticoagulation Forum recommends “administration of a reversal agent only if bleeding is life-threatening, into a critical organ or is not controlled with maximal supportive measures and there is demonstration or reasonable

expectation that the patient has clinically relevant plasma DOAC levels.”

“You don’t want to use a reversal agent if you don’t have to because it may have adverse effects, but if a patient is bleeding into the spine or pericardium or not stable, you may need to consider using one,” Minichiello advised.

For elective surgery, stopping anticoagulant therapy for two or three days will usually suffice, though patients with impaired kidney function may need longer to clear the medication. For unplanned procedures, “if you can wait, that’s ideal because the anticoagulation effect will go away. If you can’t wait and there is a clinically significant amount of anticoagulant there, you may want to use a reversal agent,” Minichiello said.

Idarucizumab is approved for presurgical use, but andexanet alfa is not, she noted. While the Anticoagulation Forum suggests that andexanet alfa could be used prior to urgent surgery, Minichiello clarified that the Forum is providing “guidance where there is no data or FDA indication. Some may opt for four-factor PCC in that situation.” 

<sup>1</sup> Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in Patients with Atrial Fibrillation. *N Engl J Med*. 2011 Mar 3;364(9):806-17.

<sup>2</sup> Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation. *N Engl J Med*. 2011 Sept 15;365:981-992.

<sup>3</sup> Piran S, Schulman S. Treatment of bleeding complications in patients on anticoagulant therapy. *Blood*. 2019;133(5):425-35.

<sup>4</sup> Kuramatsu JB, Sembill JA, Huttner HB. Reversal of oral anticoagulation in patients with acute intracerebral hemorrhage. *Crit Care*. 2019 June 6;23:206.

# POPULATION MANAGEMENT TOOL STREAMLINES DOAC MONITORING

WEST PALM BEACH, FL—Since 2011, the VA has recommended use of the healthcare system’s anticoagulation clinics to manage patients on direct acting oral anticoagulants as well as warfarin. Clinical pharmacy specialists manage these clinics, determine patient suitability for DOACs and proper dose, and educate patients on the medications.

While DOAC therapy does not require the close monitoring required for warfarin, multiple studies in the VA have found that patients monitored on the drugs by clinical pharmacists had improved appropriate dosing, drug selection, adherence, as well as, lower morbidity and mortality.

At the West Palm Beach VAMC anticoagulation clinic, about two-thirds of patients are on DOAC therapy. The clinic typically sees veterans for a personal appointment shortly after a provider prescribes a DOAC. The face-to-face visit includes education and dispensing the medication. Historically, pharmacists then phoned each patient for a scheduled 15-minute check-in at two and four weeks after initiation and every three to six months thereafter. Additional in-person appointments and laboratory testing occurred whenever the pharmacist determined one was needed.<sup>1</sup>

As physicians, pharmacists and patients have become more comfortable with DOACs, the clinic leadership developed a more efficient and less resource intensive protocol in conjunction with a DOAC Population Management Tool that flagged patients likely to need attention for a pharmacist’s review.

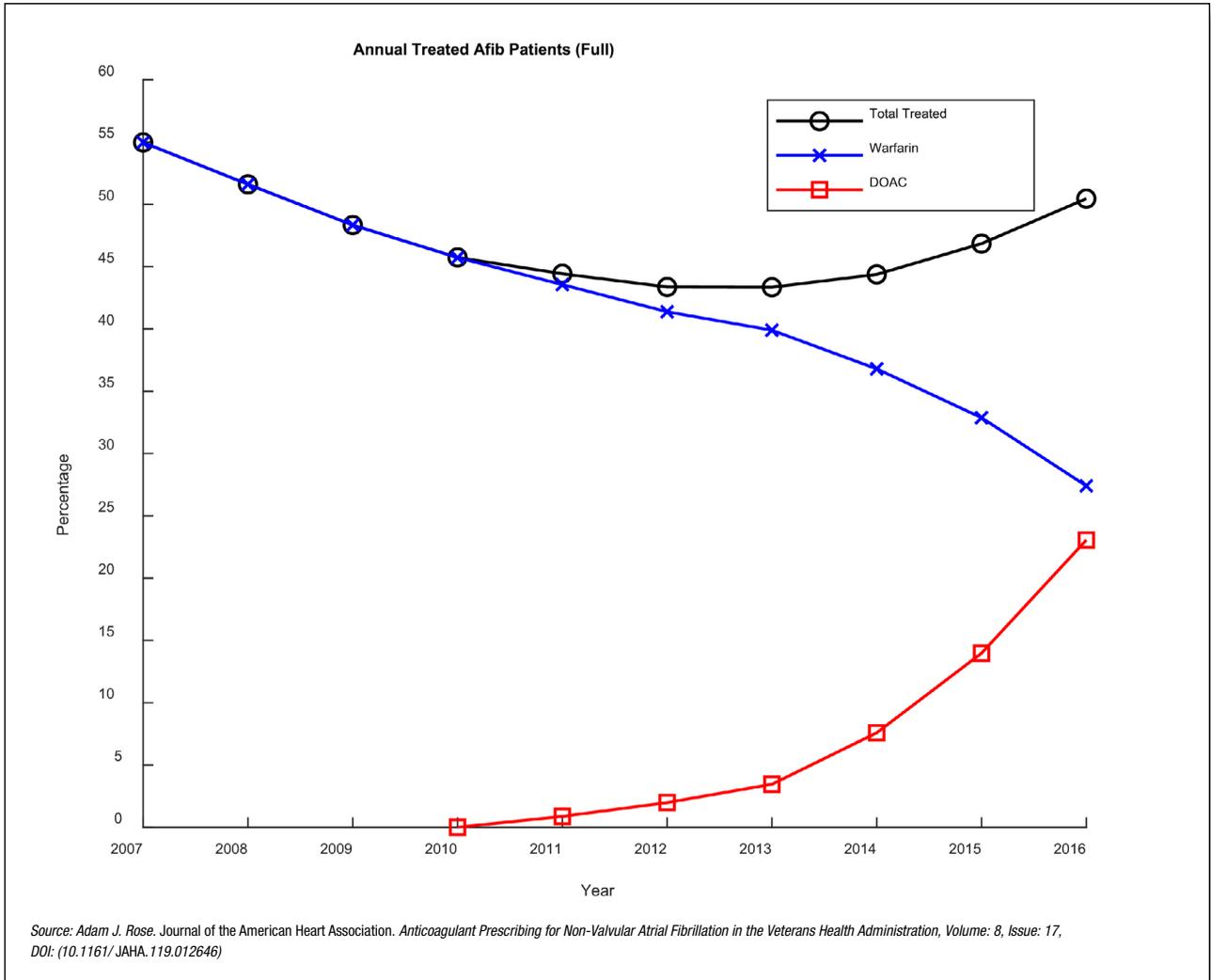
The PMT updates daily based on data gathered during standard patient care practices and alerts pharmacists that a veteran may need an intervention when results fall outside prespecified parameters. “Some parameters include drug:drug interaction, dose inappropriateness or side effects, a history of bleeding or failure to refill medications,” said Daniela

Valencia, PharmD, inpatient clinical pharmacist at the West Palm Beach VAMC.

“The clinical pharmacist reviews and assesses each flag and determines the need for clinical intervention. If needed, the patient is contacted and the interaction is documented on the patient chart as appropriate,” she told *U.S. Medicine*.

“If it’s a dosing issue or critical lab for renal function, the anticoagulation clinic provider will review it and either do a dose change by phone or determine a patient’s need to be seen in clinic,” Valencia added. Changes in medication and additional education “will be scheduled much faster than under regular practice.”

The population management tool updates daily based on data gathered during standard patient care practices and alerts pharmacists that a veteran may need an intervention when results fall outside prespecified parameters.



In a study published in the *Annals of Pharmacotherapy*, Valencia and her colleagues found that using the population management tool increased opportunities for interventions and increased clinic access for veterans who needed follow up. The study included 399 patients, of whom 131 were monitored by the population management tool and 268 received usual care. Veterans in the PMT group had a history of valve replacement or dosing issues.

During the study, the PMT flagged patient records a total of 170 times, resulting in 94 interventions or 0.55 interventions per flag. In the usual care group, pharmacists assessed 268 patients and made 53 interventions or 0.20 interventions per patient encounter. Generating an intervention took just 16 minutes for pharmacists using the PMT and more than an hour for those providing usual care.

Based on these results, the clinic implemented the PMT for

all long-term DOAC therapy monitoring.

“For broader use, implementing the DOAC PMT would help strategize DOAC use and monitoring across the VA,” Valencia said. “At a larger scale, you’d basically help reduce DOAC implementation variation across sites and allow for more timely interventions.”

<sup>1</sup> Valencia D, Soutz P, Stoppi J, et al. Impact of a Direct Oral Anticoagulant Population Management Tool on Anticoagulation Therapy Monitoring in Clinical Practice. *Ann Pharmacother*. 2019 Aug;53(8):806-811.

# FEWER DRUG REACTIONS MAKE DOACS BETTER FOR COMPLEX VA PATIENTS

IOWA CITY, IA—About one-third of VA patients have three or more chronic conditions.<sup>1</sup> Ironically, for many of them, that complexity makes choosing between warfarin and a direct acting oral anticoagulant easier.

“The presence of multiple chronic conditions often means that patients are on several prescription medications,” said Mary S. Vaughan Sarrazin, PhD, investigator, Center for Access and Delivery Research and Evaluation based at the Iowa City VAMC, and associate professor of internal medicine at the Roy and Lucille J. Carver College of Medicine at the University of Iowa. “DOACs are believed to have fewer interactions with other drugs than warfarin, which may make them safer for patients with very complex medication regimens.”

Some conditions may make the decision to use any anticoagulant more fraught, however. “Some patients may have conditions that impact both bleeding and stroke risk. In those patients, it may be difficult to determine whether the benefits of improved stroke prevention outweigh the increased risk of dangerous hemorrhage associated with anticoagulants,” she told *U.S. Medicine*.

While the U.S. Food and Drug Administration provides guidance

for anticoagulant choice in the presence of renal disease, guidelines are “not explicit with respect to anticoagulation therapy in patients with more complex illness,” she said.

To help clinicians determine the best choice for patients with multiple comorbidities, Sarrazin and her colleagues at the Carver College of Medicine evaluated the outcomes of treatment with warfarin and the DOACs dabigatran and rivaroxaban in nearly 22,000 Medicare patients diagnosed with atrial fibrillation between 2010 and 2013.<sup>2</sup>

The team found no difference in stroke rates between the three medications.

Dabigatran had a 38% lower risk of major hemorrhage compared to warfarin in patients with a low Gagne comorbidity score and similar risk of major bleeding in patients with moderate to high comorbidity scores. Rivaroxaban had similar rates of major hemorrhage compared to warfarin in all groups but higher risk compared to dabigatran in patients with medium and high morbidity scores.

Both rivaroxaban and dabigatran users had significantly lower mortality risk than warfarin users.

Because the DOACs apixaban and edoxaban came on the market after the start of the study, the researchers did not include them

*“Current VA guidelines suggest that physicians consider apixaban over other DOACs in patients with a history of bleeding or factors associated with increased risk of bleeding.”*



— Mary S. Vaughan Sarrazin, PhD  
Investigator, Center for Access and Delivery Research and Evaluation, Iowa City VAMC

**Table 1: The 8 A's – drugs that interact with warfarin\***

Drug or drug class	Risk of hemorrhage	Mechanism
<b>Antibiotics</b>		
Most agents, but especially co-trimoxazole, metronidazole, macrolides and fluoroquinolones	↑	Inhibition of vitamin K synthesis by intestinal flora, inhibition of hepatic warfarin metabolism, or both
Rifampin	↓	Induction of cytochrome P450 (CYP) isoenzyme 2C9
<b>Antifungals</b>		
Fluconazole, miconazole	↑	Inhibition of CYP 2C9
<b>Antidepressants</b>		
Serotonergic agents (selective serotonin reuptake inhibitors)	↑	Interference with primary hemostasis; some (e.g., fluoxetine) also inhibit CYP 2C9
<b>Antiplatelet agents</b>		
Acetylsalicylic acid, clopidogrel, ticlopidine	↑	Interference with primary hemostasis
Amiodarone	↑	Inhibition of CYP 2C9
<b>Anti-inflammatory agents</b>		
All, including selective cyclooxygenase-2 inhibitors	↑	Direct mucosal injury; interference with primary hemostasis may also play a role
<b>Acetaminophen</b>		
	↑	Direct interference with vitamin K cycle
<b>Alternative remedies</b>		
<i>Ginkgo biloba</i> , dong quai, fenugreek, chamomile	↑	Multiple and often incompletely characterized
St. John's wort	↓	Multiple and often incompletely characterized

\*This is only a partial list of drugs that can alter the response to warfarin. A more detailed discussion is given in references 4 and 5. Of note, some patients exposed to specific drug combinations will exhibit no interaction, in part because pharmacogenetics and other factors govern the expression of many interactions.

Source: *CMAJ* August 14, 2007 177 (4) 369-371; DOI: <https://doi.org/10.1503/cmaj.0709>

in the analysis, but they are likely to have similar results. “Clinical trials for apixaban and edoxaban both found a mortality advantage over warfarin,” Sarrazin said. “While results from clinical trials do not always translate to clinical practice, we have no reason to believe that the same mortality advantage would not exist in clinical practice.”

Several clinical trials have demonstrated a lower risk of bleeding for apixaban than other DOACs and warfarin “Edoxaban, dabigatran and rivaroxaban have been shown to have higher risk of gastrointestinal bleeding compared to

warfarin. Current VA guidelines suggest that physicians consider apixaban over other DOACs in patients with a history of bleeding or factors associated with increased risk of bleeding,” she added.

Still, warfarin may be the best option for some patients. “There’s an increasing trend of DOAC use in VA,” Sarrazin noted. “However, warfarin is still recommended for patients with severe renal impairment or patients with mechanical heart valves. Moreover, DOACs may have intolerable side effects such as dyspepsia—making warfarin a more tolerable option.

Finally, physicians and patients may prefer the monthly monitoring required with warfarin use to assess anticoagulant activity in complex patients where relative risks and benefits of anticoagulation are particularly unclear.”

<sup>1</sup> Yoon J, Zulman D, Scott JY, Maciejewski ML. Costs associated with multimorbidity among VA patients. *Med Care*. 2014 Mar;52 Suppl 3:S31-36.

<sup>2</sup> Mentias A, Shantha G, Chaudhury P, Sarrazin MS. Assessment of Outcomes of Treatment with Oral anticoagulants in patients with Atrial Fibrillation and Multiple Chronic Conditions: A Comparative Effectiveness Analysis. *JAMA Netw Open*. 2018 Sept 7;1(5):e182870.

