PHARMACIST CE:

The X-Factor: Overcoming DOAC Barriers in OAC Eligible Patients

by Christi Ann Albert, PharmD, BCPS, Kristina Yokes, PharmD, BCACP, Anne E. Rose, PharmD

Direct oral anticoagulants (DOACs) have emerged as a preferred anticoagulant in eligible patients who have atrial fibrillation (AF) or venous thromboembolism (VTE).[1-3] Prior to DOACs, anticoagulation options included vitamin K antagonists (VKAs) and parenteral agents. DOACs are now recommended over VKAs by societal guidelines given their efficacy and improved or similar bleeding risks compared to VKAs.[1-3] DOACs offer key advantages, such as rapid onset, few drug-drug interactions, and limited dietary interactions. However, potential barriers exist, including cost and provider/patient knowledge of a newer class of medications (Table 1).

Warfarin, a vitamin K antagonist,

CE FOR **PHARMACISTS**

COMPLETE ARTICLE AND CE EXAM AVAILABLE ONLINE: **WWW.PSWI.ORG**

Learning Objectives

- Identify patient populations eligible for DOACs and when DOAC use is controversial or contraindicated.
- Compare and contrast characteristics of VKAs with DOACs.
- Apply national organizational guidelines for AF and VTE when choosing an anticoagulant.
- Describe ways to overcome cost barriers for DOACs.

Abbreviations

ACC - American College of Cardiology
AF - atrial fibrillation
AHA - American Heart Association
DOAC - direct oral anticoagulant
DVT - deep vein thrombosis
HRS - Heart Rhythm Society
OAC - oral anticoagulant
PE - pulmonary embolism
VKA - vitamin K antagonist
VTE - venous thromboembolism

TABLE 1. Oral anticoagulant options: Comparing VKA to DOACs

Warfarin (Coumadin®)		*Direct Oral Anticoagulants (Eliquis®, Xarelto®, Pradaxa®, Savaysa®)*	
⚠	No longer first line option for AF or VTE	✓	Preferred first line option for AF and VTE given efficacy and lower overall rates of intracranial hemorrhage.
✓	> 60 years' experience with many indications	⚠	Fewer approved indications – still waiting for data in some conditions that could cause stroke or thromboembolism
✓	Ability to check INRs as a measure of efficacy/safety	✓	No need for frequent drug-levels
⚠	Narrow therapeutic range – Poor outcomes associated with out-of-range INRs or low time in therapeutic range (TTR ≤ 65%)[17]	✓	Wide therapeutic index
⚠	Many drug-drug interactions including herbal supplements and over-the-counter medications	✓	Fewer drug interactions
✓	Effect of any drug interaction can be monitored with INR testing and dose adjustments can be made to accommodate interaction	✗	Phenobarbital, phenytoin, carbamazepine, St John's Wort, and rifampin are contraindicated with DOACs
⚠	Need for consistent diet (vitamin K containing foods, alcohol, cranberry juice, grapefruit juice all affect INR)	✓	Almost no dietary interactions outside of grapefruit juice and alcohol
✓	Readily reversible with phytonadione (vitamin K) or prothrombin complex concentrates (PCC)	✓	Reversal agents for severe bleeding are available (including prothrombin complex concentrates (PCCs), andexanent alfa (Andexxa®) and idarucizumab (Praxbind®)
⚠	Variable dosing that can change with each INR	✓	Consistent dosing with infrequent dose adjustments
✓	Inexpensive	⚠	Can be cost prohibitive for some patients. Manufacturer and industry sponsored assistance programs are available to offset higher upfront cost

AF = atrial fibrillation; VTE = venous thromboembolism; DOAC = direct oral anticoagulant

was initially approved in 1954.[4] It acts by inhibiting the synthesis of Vitamin-K dependent clotting factors, which include Factors II, VII, IX, and X, along with proteins C and S.[4] In 2010, dabigatran (Pradaxa®) was the first DOAC approved by the Food and Drug Administration (FDA) in the United States.[5] Dabigatran is a direct thrombin inhibitor, which prevents the conversion of fibrinogen to fibrin.[5] Factor Xa inhibitors followed, which prevent clot formation by decreasing thrombin generation. These include rivaroxaban (Xarelto®) in 2011, apixaban (Eliquis®) in 2012, and edoxaban (Sayvasa®) in 2015.[6-8]

Notably, there are some patient populations where DOACs are contraindicated or where the risk/benefit should be discussed prior to use (Figure 1).[9] This article focuses on the two most common indications for DOACs, AF and venous thromboembolism (VTE), by providing clinical rationale along with strategies to overcome barriers to DOAC usage.

Atrial Fibrillation

Atrial fibrillation (AF) is one of the most common arrythmias prevalent worldwide and is responsible for 15% of strokes.[10,11] Patients with AF have a 5-fold increased risk of stroke when compared to patients without AF. AF-induced thromboembolic strokes are associated with increased morbidity, mortality, and costs when compared to strokes from other causes. Given the rates of obesity and diabetes, along with an aging population, projections estimate that the prevalence of AF will at least double in the next 25 years.

Figure 2 outlines the different types of AF.[12] Older guidelines classified AF as either valvular or nonvalvular AF.[1] Newer versions of published guidelines are transitioning to new terminology, which focuses on cause and length of time AF is present. The guidelines state oral anticoagulants (OAC) should be considered for atrial flutter or AF including paroxysmal, permanent, and chronic (also called long-standing).

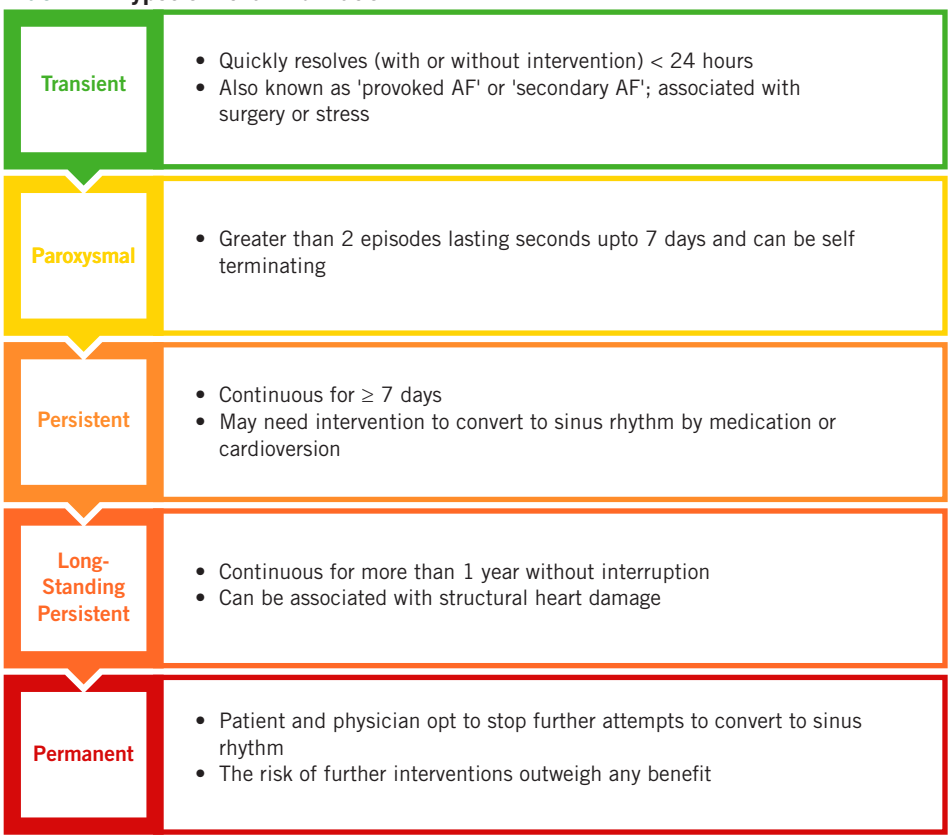
The risk of stroke from AF can be calculated using a risk assessment tool. Previous recommendations by the American Heart Association, American College of Cardiology and Heart Rhythm Society (AHA/ACC/HRS) Atrial Fibrillation Guidelines ("the AF Guidelines") had been

FIGURE 1. Contraindicated or Controversial DOAC Use[1-9]

DOAC Use is Contraindicated
Indications in which DOACs have proven harmful or inefficacious • Mechanical heart valve replacement • Left Ventricular Assist Device (LVAD) • Triple Positive Antiphospholipid Antibody Syndrome (APS) • Embolic Stroke of Undetermined Source (ESUS) • Moderate to Severe Mitral Valve Stenosis
Within 3 months of bioprosthetic heart valve replacement
Severe hepatic impairment
Pregnancy or breastfeeding
Female (sex assigned at birth) of childbearing potential not using reliable contraception
Taking medications known to majorly interact with DOACs*
Unable to access DOAC due to cost without access to financial assistance
DOAC Use is Controversial (Discuss Risk/Benefits Prior to Use)
Off-label indications
VTE associated with gastrointestinal (GI) or genitourinary (GU) cancers
Moderate hepatic impairment
Severe renal impairment (CrCl<30mL/min)**
Taking multiple inhibitors of DOAC metabolism in setting of moderate impaired renal function
Poor medication adherence
Treatment failure on therapeutic warfarin or low molecular weight heparin
History of gastric bypass or removed portions of GI tract

**Phenytoin, carbamazepine, phenobarbital, St John's Wort, Rifampin are examples*
***indication and DOAC dependent*
DOAC = direct oral anticoagulant; CrCl - creatinine clearance; GI = gastrointestinal; VTE = venous thromboembolism
Reproduced with permission from the 2021 DOAC Playbook - Anticoagulation Forum©
Adapted to incorporate 2019 AHA/ACC/HRS AF Guidelines

FIGURE 2. Types of Atrial Fibrillation



Adapted from Healthline – Types of Atrial Fibrillation[12]. AF = atrial fibrillation

to use the $CHADS_2$ score.[1,13] The updated 2014 and revised 2019 AF Guidelines now recommend using the CHA_2DS_2VASc score to better identify at-risk patients. Criteria are outlined in Table 2. The changes from the $CHADS_2$ to the CHA_2DS_2VASc scoring tool includes 1 point for history of vascular diseases, including coronary artery disease (CAD), myocardial infarction (MI), coronary artery bypass grafting (CABG), cardiac stents or percutaneous coronary interventions (PCI), peripheral vascular disease (PVD), or venous stasis. The tool also includes 1 point for younger ages 65-74 years, and 1 point for female (sex assigned at birth). Female sex is a singular risk factor in the CHA_2DS_2VASc score and should not be considered without other risk factors for stroke. The female sex risk factor is age dependent and further impacts stroke risk starting at age 65. The change to utilizing the CHA_2DS_2VASc score has increased the proportion of people eligible for oral anticoagulation by 20%.[13,14] The updated 2019 AF guidelines strongly recommend oral anticoagulation (Level 1A recommendation; strongest strength and highest quality evidence) for any CHA_2DS_2VASc score ≥ 2 for men and ≥ 3 for women.[1] A notable change is that aspirin is no longer recommended for CHA_2DS_2VASc scores of 1 for men and 2 for women; therefore, OACs may be considered (Level 2b/C recommendation; weak benefit based on limited data) since there is a net positive clinical benefit of anticoagulation. Thus, females with AF and CHA_2DS_2VASc scores ≥ 2 remain OAC eligible, and for brevity, we will refer to any sex patient with AF and CHA_2DS_2VASc score ≥ 2 as OAC eligible.

Despite current guidelines recommending anticoagulation for patients with AF and CHA_2DS_2VASc scores ≥ 2, as many as 30%-40% of patients are not prescribed anticoagulation.[10,15] In half of these cases, it is provider preference not to anticoagulate.[10] The underuse of anticoagulation has been well studied and is multifactorial. Provider-perceived factors include patient fall risk, past recurrent falls, advanced age, perceived bleeding risks, cost and/or socioeconomic status, patient/provider spoken language mismatch, transportation barriers and/or rural residency, and prior or anticipated poor adherence and/or follow-up.[15,16] Other factors include under-diagnosis or lack of documentation of AF; lack of clarity if AF diagnosis is transient or temporary; lack of a documented CHA_2DS_2VASc score; provider practice area; provider familiarity with AF guideline recommendations; under-estimation of risk of stroke or overestimation of risk of bleeding.[10] Additionally, approximately 25% of patients within the first year of warfarin therapy for AF in the ATRIA study discontinued therapy, and this was a similar outcome in the ORBIT-AF registry.[18,19] Reasons for anticoagulation discontinuation

TABLE 2. Managing AF based on CHA_2DS_2VASc Scores and Thromboembolic/Stroke Risk[1,13]

Calculate CHA_2DS_2VASc Score: Add points in parenthesis for each applicable risk factor:
- Age (65-74=1; ≥75=2)
- Sex (Female=1)^
- CHF (1)
- HTN (1)
- DM (1)
- Vascular History (History of MI/CAD/CABG/Stenting/PCI, vascular disease, vascular plaques 1)
- History of stroke/TIA/ thromboembolism (2)

ACC/AHA/HRS OAC Guidance	*CHA_2DS_2VASc Score*	*Risk of stroke, TIA, systemic embolism*	
No OAC	0	Low	0.3%
OAC Eligible (Male^)	1		0.9%
OAC Eligible (Female^)	2	High	2.9%
OAC Recommended	3		4.6%
	4		6.7%
	5		10.0%
	6		13.6%
	7		15.7%
	8		15.2%
	9		17.4%

ACC/AHA/HRS 2019 AF Guideline Update no longer recommends aspirin as an alternative to OAC therapy no matter the CHA_2DS_2VASc risk score
- Omit OAC therapy for CHA_2DS_2VASc score = 0 male and ≤ 1 female^
- OAC Eligible for CHA_2DS_2VASc score = 1 for male and = 2 for female^
- OACs Recommended for CHA_2DS_2VASc score ≥ 2 for male and ≥ 3 for female^

^ Male / female sex refers to sex assigned at birth

Abbreviations: CHF=congestive heart failure, HTN=hypertension, DM=diabetes mellitus, MI=myocardial infarction, CAD=coronary artery disease, CABG=coronary artery bypass graft, PCI=percutaneous coronary intervention, TIA=transient ischemic attack, OAC=oral anticoagulant.

Adapted from 2019 ACC/AHA/HRS AF Guideline & Table 2 from Friberg L, Rosenqvist M, Lip GY. Eur Heart J. 2012;33(12):1500-1510

TABLE 3. Comparison of Prospective AF DOAC Trials[21-24]

Comparison Prospective AF DOAC trial efficacy outcomes				
	ARISTOTLE (apixaban)	*ROCKET-AF (rivaroxaban)*	*RE-LY (dabigatran)*	*ENGAGE AF-TIMI 48 (edoxaban)*
Composite – systemic embolism or stroke	**Superior**	Non-inferior	**Superior**	Non-inferior
Comparison Prospective AF DOAC trial safety outcomes				
Major bleeding	**Superior**	Non-inferior	Non-inferior	**Superior**
Intracranial hemorrhage (ICH)	**Superior**	**Superior**	**Superior**	**Superior**

included provider preference (47%), patient preference (21.1%), bleeding events (20.2%), frailty (10.8%), perceived high bleeding risk (9.8%), and poor adherence (4.7%).

Due to the low national adherence to guideline-based recommendations, AHA/HRS have started a quality improvement program called Get with the Guidelines (GWTG).[20] There are GWTG programs for multiple cardiovascular disease states, including GWTG-Coronary Artery Disease, GWTG-Heart Failure, and now GWTG-AFIB. The GWTG-AFIB quality improvement program started in 2013. Hospitals and health systems registered with the program and were provided with materials for providers and patients to facilitate guideline adherence. The GWTG-AFIB study participants were able to increase OAC prescribing in AF from a baseline of 60% (near the national average) to 90% after 18 months, and 95% after 4 years following enrollment into the program. Of the remaining 5% of patients not anticoagulated, the majority represented those with absolute contraindications to anticoagulation: prior major life-threatening bleeding, prior intracranial hemorrhage (ICH), recent high bleed risk operation, or severe critical comorbid illness (patients on comfort cares were excluded). The implementation of quality-based GWTG-AFIB was able to reduce the proportion of patients and providers who previously either had a preference against anticoagulation or who previously discontinued to as low as 2.7% and 2.6% respectively. The total of all prior stated contraindications to anticoagulation were in sum reduced from 20.9% to 12.9% over the four-year study period.

The 2019 AF Guidelines now recommend anticoagulation with DOACs over warfarin in eligible patients.[1] The preference for DOACs over warfarin is listed as a level 1A (strongest strength and highest quality evidence) recommendation. The guideline draws these conclusions from the primary AF DOAC drug trials, which cumulatively have included over 70,000 patients: ARISTOTLE (apixaban versus warfarin in AF), RE-LY (dabigatran versus warfarin in AF), ROCKET-AF (rivaroxaban versus warfarin in AF) and ENGAGE AF-TIMI48 (edoxaban versus warfarin in AF) and have demonstrated on average 50% reduced rate of intracranial hemorrhage, statistically significant reduced rates of bleeding, and improved mortality.[21-24] The clinical outcomes of these individual drug studies when compared to warfarin are listed in Table 3.

The risk of stroke is up to 20 times higher in the setting of combined AF and severe mitral stenosis.[1,10] However, AF caused by moderate to severe mitral valve stenosis and mechanical heart valves are considered contraindications to

TABLE 4. ARISTOPHANES Observational Data Summary[30]

	*Outcome**	*apixaban vs. warfarin*	*rivaroxaban vs. warfarin*	*dabigatran vs. warfarin*	*apixaban vs. rivaroxaban*	*apixaban vs. dabigatran*	*dabigatran vs. rivaroxaban*
Efficacy	Stroke / systemic embolism (SSE)	697 (1.33) vs. 1,299 (1.92)	1,203 (1.51) vs. 1,593 (2.21)	333 (1.42) vs. 428 (1.74)	710 (1.28) vs. 1,008 (1.47)	215 (1.12) vs. 333 (1.43)	334 (1.42) vs. 309 (1.29)
	Hazard Ratio (SSE)	0.64 [0.58-0.70]	0.79 [0.73-0.85]	0.82 [0.71-0.95]	0.80 [0.73-0.89]	0.72 [0.60-0.85]	1.10 [0.95-1.23]
Safety	Major Bleed (MB)	1,902 (1.77) vs. 3,770 (5.63)	4,607 (5.83) vs. 4,541 (5.45)	832 (3.60) vs. 1,229 (5.05)	1,948 (3.52) vs. 3,981 (5.88)	571 (2.98) vs. 832 (3.58)	836 (3.57) vs. 1,190 (5.02)
	MB Hazard Ratio	0.60 [0.56-0.63]	1.06 [1.02-1.10]	0.71 [0.65-0.78]	0.55 [0.53-0.59]	0.78 [0.70-0.87]	0.71 [0.65-0.78]
	Intracranial hemorrhage (ICH)	84 (0.36) vs. 210 (0.85)	452 (0.57) vs. 750 (0.89)	84 (0.36) vs. 210 (0.85)	272 (0.49) vs. 375 (0.55)	77 (0.40) vs. 85 (0.36)	85 (0.36) vs. 115 (0.48)
	Hazard Ratio (ICH)	0.56 [0.48-0.65]	0.63 [0.56-0.71]	0.43 [0.33-0.55]	0.86 [0.73-1.00]	1.04 [0.76-1.42]	0.75 [0.57-1.00]
	*Outcome***	*apixaban (n=100,977) vs. warfarin (n=100,977)*	*rivaroxaban (n=125,068) vs. warfarin (n=125,068)*	*dabigatran (n=36,990) vs. warfarin (n=36,990)*	*apixaban vs. (n=107,236) rivaroxaban (n=107,236)*	*apixaban vs. (n=37,314) dabigatran (n=37,724)*	*dabigatran vs. (n=37,724) rivaroxaban (n=37,724)*
Mortality	Death	2,730 (6.81) vs. 5,036 (9.63)	4,343 (7.11) vs. 5,867 (9.08)	932 (5.68) vs. 1,414 (8.15)	2,692 (6.56) vs. 3,704 (7.23)	762 (5.79) vs. 932 (5.69)	933 (5.69) vs. 1,050 (6.39)
	Hazard Ratio	0.65 [0.62-0.68]	0.78 [0.75-0.81]	0.70 [0.64-0.76]	0.84 [0.80-0.89]	0.97 [0.88-1.06]	0.89 [0.82-0.97]

Numbers of events (Rates per 100-person-years)
**Propensity score-matched cohorts*
***CMS Medicare Population among propensity score-matched cohorts (data subset)*
Adapted from ARISOTOPHANES Figure 2 and Supplemental Tables XII and XIII.
Numbers of events (Rates per 100-person-years)

DOAC therapy.[1] This recommendation is extrapolated from the RE-ALIGN trial comparing dabigatran to warfarin in patients with mechanical heart valves.[25] The study was stopped early as dabigatran was shown to have increased risk of stroke and mortality.

AF guidelines consider apixaban, the DOAC with lowest renal elimination at 27%, to be a reasonable alternative (Level 2b/B recommendation; weak benefit moderate qualify of evidence) to warfarin for the patient with renal impairment as well as end-stage renal disease (ESRD) and dialysis.[1,7,26] Apixaban has an FDA approval for use in patients with concomitant AF and ESRD and/or dialysis from a small, single-dosed single-dosed pharmacokinetic (PK) study of 8 patients.[27] Notably, apixaban is not dialyzable either via peritoneal or hemodialysis nor requires dose adjustments in hemodialysis.[7] Additional retrospective data from 2,300 dialysis patients on apixaban compared to 25,000 warfarin patients demonstrated lower overall bleeding rates with apixaban (HR 0.71, 0.59-0.87, P< 0.001), but rates of stroke and embolism (HR 0.88; 0.69-1.12) were not statistically significantly lower. However, half of patients in the apixaban arm were prescribed the lower 2.5mg BID dose in comparison to the standard 5mg BID dose.[7,26] Pending prospective RCTs to evaluate this include RENAL-AF (Trial to Evaluate Anticoagulation Therapy in Hemodialysis Patients with Atrial Fibrillation), which will randomize patients to apixaban 5mg BID or warfarin, and the AXADIA study (Compare Apixaban and Vitamin-K Antagonists in Patients with Atrial Fibrillation and End-Stage Kidney Disease), which will randomize patients to apixaban 2.5 mg BID versus a vitamin K antagonist.[28]

Similarly, rivaroxaban also has a small, single-dose PK study of 32 patients, 24 of whom had varying degrees of renal function but were not on renal replacement therapies, who received one 10 mg dose of rivaroxaban. PK data showed a decrease in rivaroxaban clearance but only moderately impactful even in those with creatinine clearance less than 30 mL/min.[29] Despite this PK data, AF Guidelines refer to the use of rivaroxaban (as well as dabigatran and edoxaban) in end-stage CKD or dialysis to be a Level 3/C-EO recommendation (data lacks to prove that benefit exceeds risk based on expert opinion). Rivaroxaban, dabigatran, and edoxaban can, however, be considered in mild to moderate renal impairment per the package labeling and is a Level 2b/B recommendation in AF Guidelines (weak benefits outweigh risks with moderate quality evidence).[1,6,8,9]

TABLE 5. Comparison of Prospective DOAC Acute VTE Trials[34-39]

	AMPLIFY (apixaban)	EINSTEIN-DVT, EINSTEIN-PE (rivaroxaban)	RE-COVER, RE-COVER II (dabigatran)	HOKUSAI-VTE (edoxaban)
Efficacy outcomes for acute VTE treatment				
Recurrent VTE or VTE-related death	Non-inferior	Non-inferior	Non-inferior	Non-inferior
Safety outcomes for acute VTE treatment				
First major or clinically relevant non-major bleeding event	**Superior**	Non-inferior	**Superior**	**Superior**

VTE = venous thromboembolism

While there are no prospective studies comparing DOACs in head-to-head randomized controlled trials (RCTs), the ARISTOPHANES (Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients) study is one of the largest observational claims-based studies pooling DOAC use in over 280,000 patients with atrial fibrillation.[30] Stroke, systemic embolism, and major bleeding were efficacy and safety end points and results are in Table 4.

Most patients included in ARISTOPHANES were on either warfarin (n=167,413) or rivaroxaban (n=153,002), followed by apixaban (n=108,852), and dabigatran (n=37,724). The patient demographics, comorbidities, CHA_2DS_2VASc scores, HAS-BLED scores were balanced between study arms. Approximately 75%-85% of patients prescribed a DOAC were on full dose therapy (77.5% apixaban, 84.6% dabigatran, and 72.1% rivaroxaban) with the remainder of patients on lower dose therapy. Patients prescribed lower dose therapy corresponded well with the rates of reported renal disease (23%, 16%, and 20% with apixaban, dabigatran and rivaroxaban respectively).

The ARISTOPHANES study, while observational, cumulatively triples the number of patients studied in original DOAC AF RCTs. ARISTOPHANES further supports original DOAC study findings that apixaban and dabigatran are both superior to warfarin in both efficacy and bleeding with the data favoring apixaban. In ARISTOPHANES, rivaroxaban demonstrates improved efficacy outcomes in comparison to ROCKET-AF in which rivaroxaban performed about similarly (non-inferior) to warfarin. The bleeding rate with rivaroxaban use, while similar to warfarin, appears to be higher than when compared either apixaban or dabigatran. Since data from ARISTOPHANES is observational, caution should be used when drawing conclusions between DOACs. Current DOAC to DOAC prospective RCTs in process include DARING-AF (Comparison of Efficacy and Safety among Dabigatran, Rivaroxaban, and Apixaban in Nonvalvular Atrial Fibrillation) and DANNOAC-AF (The Danish Non-Vitamin K Antagonist Oral Anticoagulation Study: A Cluster Randomized Study Comparing Safety and Efficacy of Edoxaban, Apixaban, Rivaroxaban and Dabigatran for Oral Anticoagulation in Atrial Fibrillation).[31,32]

Venous Thromboembolism

VTE encompasses pulmonary embolism (PE) and deep vein thrombosis (DVT). In the United States, up to 900,000 people are affected by VTE events annually.[33] It is fatal for 10%-30% of people within one month of diagnosis.[33] Prompt initiation of an anticoagulant is crucial to prevent VTE recurrence and VTE-related death. While warfarin has been the oral anticoagulant treatment for VTE for decades, DOACs have now emerged as a preferred anticoagulant for eligible patients.[2,3]

Two national organizations have

released recent guidelines for management of VTE. In 2020, the American Society of Hematologists (ASH) published "American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism."[2] In 2021, CHEST updated their guideline "Antithrombotic Therapy for VTE Disease: Second Update of the CHEST Guideline and Expert Panel Report."[3] Key guidance statements and recommendations pertaining to DOACs in non-surgical, non-cancer patients are reviewed in this article.

Initiation and Treatment Phase

The approach to treatment of VTE is separated into two phases. The initial phase refers to the time period where anticoagulants are given after VTE diagnosis and lasts up to 5-21 days, based on which anticoagulant is selected.[2,3] The treatment phase lasts for a minimum of 3 months following the initial phase.[2,3] Apixaban and rivaroxaban can be used as monotherapy choices in both the initial and treatment phase.[6,7] Edoxaban and dabigatran require a parenteral anticoagulant for 5-10 days prior to starting either agent.[5,8] After the initial treatment with a parenteral anticoagulant is completed, edoxaban or dabigatran can be used as monotherapy for the treatment phase.[5,8] It is crucial that the correct DOAC doses are used for proper treatment of VTE (Figure 3).

Direct comparisons of DOACs for VTE is limited. Some factors in choosing a DOAC may be dependent on cost, renal function, once vs twice daily dosing, age, drug interactions and/or requirement for lead-in parenteral anticoagulation. The CHEST guidelines suggest that apixaban may offer a lower bleeding risk than other DOACs but do not make a formal recommendation on DOAC preference.[3] ASH guidelines state: "For patients with DVT and/or PE, the ASH guideline panel does not suggest 1 DOAC over another (conditional recommendation based on very low certainty in the evidence of comparative effects)."[2]

Key trials to evaluate the safety and efficacy of DOACs for use in VTE include RE-COVER/RE-COVER II (dabigatran), AMPLIFY (apixaban), EINSTEIN-DVT/EINSTEIN-PE (rivaroxaban), and HOKUSAI-VTE (edoxaban).[34-39] The overall findings of these studies are listed in Table 5.

FIGURE 3. DOAC Dosing[5-9]

	apixaban	*rivaroxaban*	*dabigatran*	*edoxaban*
Treatment of acute DVT and/or PE	10mg BID x 7 days then 5mg BID^	15mg BID x 21 days then 20mg daily with largest meal of day^	150mg BID AFTER 5-10 days of parenteral lead-in^	60mg daily AFTER 5-10 days of parenteral lead-in *^
Reduction of risk of recurrent DVT and/or PE	2.5mg BID after 6 months of initial treatment^	10mg daily after 6 months of initial treatment^	150mg BID after initial treatment^	Not FDA approved for this indication
Atrial Fibrillation	5mg BID 2.5mg BID if 2 of the following: • age ≥80 • weight < 60 kg • SCr ≥ 1.5	20mg daily with largest meal of day*^	150mg BID*^	60mg daily*^+

**requires renal dosing adjustment for CrCl 15-50 mL/min, refer to PI for details*
^avoid use in severe renal impairment CrCl <30 mL/min
+ avoid use if CrCl > 95 mL/min
Abbreviations: BID (twice daily), DVT (deep vein thrombosis), kg (kilogram), PE (pulmonary embolism), SCr (serum creatinine)
Adapted and reproduced with permission from The 2021 DOAC Playbook - Anticoagulation Forum©

Both 2020 ASH and 2021 CHEST VTE guidelines favor DOACs over VKA in the treatment phase:

- ASH: "For patients with DVT and/or PE, the ASH guideline panel suggests using direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) (conditional recommendation based on moderate certainty in the evidence of effects). Remarks: This recommendation may not apply to certain subgroups of patients, such as those with renal insufficiency (creatinine clearance, 30 mL/min), moderate to severe liver disease, or antiphospholipid syndrome".[2]
- CHEST: "In patients with VTE (DVT of the leg or PE) we recommend apixaban, dabigatran, edoxaban, or rivaroxaban over vitamin K antagonist (VKA) as treatment-phase (first 3 months) anticoagulant therapy (strong recommendation, moderate-certainty evidence)".[3] The 2021 CHEST update increased the previous GRADE of recommendation from weak recommendation, moderate-quality evidence to strong recommendation, moderate-quality evidence.

Extended Treatment Phase

In patients with an unprovoked VTE event, estimates of VTE recurrence after discontinuation of anticoagulation is 10% after one year, 25% after five years and 36% after 10 years.[40] An individualized risk/benefit analysis of continuing anticoagulation should be performed after the treatment phase and periodically thereafter. Aspects to consider include risk factors for recurrent VTE (transient or persistent), age, renal/liver function, past bleeding history, current bleeding risks and patient preference.[40]

If the decision is made to continue anticoagulation after treatment phase dosing, DOACs that have been evaluated for secondary prevention include apixaban, dabigatran, and rivaroxaban. Edoxaban is not FDA-approved for extended treatment. The AMPLIFY-EXT (apixaban), RE-SONATE (dabigatran) and EINSTEIN-EXTENSION (rivaroxaban) trials demonstrated superiority in preventing symptomatic recurrent DVT compared to placebo without a significant increase in major bleeding.[41-43] When compared to warfarin, the RE-MEDY (dabigatran) trial was noninferior to warfarin in preventing recurrent DVT with significantly lower rates of bleeding.[42]

If anticoagulation is extended, the anticoagulant dose should be re-evaluated. Dabigatran dosing remains the same. Apixaban can be reduced from 5mg twice daily to 2.5mg twice daily based on the

AMPLIFY- EXT trial.[41] Rivaroxaban can be reduced from 20mg once daily with food to 10mg daily with or without food based on the EINSTEIN-CHOICE trial.[44] However, the patients in those two studies did not have strong indications for indefinite anticoagulation and were not designed or powered to evaluate noninferiority of efficacy and superiority of safety with reduced dose DOAC compared to full dose DOAC.

Both ASH and CHEST VTE guidelines address reduced-dose DOAC based on available evidence:

- ASH: "For patients with DVT and/or PE who have completed primary treatment and will continue with a DOAC for secondary prevention, the ASH guideline panel suggests using a standard-dose DOAC or a lower-dose DOAC (conditional recommendation based on moderate certainty in the evidence of effects)".[2]
- CHEST: "In patients offered extended-phase anticoagulation, we suggest the use of reduced-dose apixaban or rivaroxaban over full-dose apixaban or rivaroxaban (weak recommendation, very low certainty evidence)."[3]

Importantly, the RENOVE study (REduced Dose Versus Full-dose of Direct Oral Anticoagulant After uNprOvoked Venous thromboembolism) is currently underway with expected completion date of October 2023.[45] It is a randomized, parallel arm, controlled trial with an estimate 2200 participants. Their hypothesis is "After VTE at high risk of recurrence initially treated during 6 (-15 days) to 24 (+ 3 months) uninterrupted months, a reduced dose of DOAC will be non-inferior to a full dose of DOAC in terms of recurrent VTE during extended anticoagulation phase." The results of this study will give more insight into whether DOAC doses should be reduced or not during extended phase anticoagulation treatment.

Barriers to DOAC Use

The decision to start anticoagulation and the selection of anticoagulant should ideally be accomplished through shared decision-making with the patient.[1,46,47] This approach is more collaborative and conversational in comparison to past prescriptive practices. While guidelines, studies, and data favor a DOAC over VKA for most patients with VTE or AF, there can be potential barriers preventing DOAC use. Lack of provider clinical knowledge or perceptions of OAC options, along with financial challenges, are some of the top concerns.[48]

Prescription claims data can give insight into OAC prescribing trends. The most recent Medicare Provider Utilization and Payment Data from 2013-2018 was retrospectively analyzed to evaluate OAC prescribing in the United States.[49] Over the study period, warfarin prescription volume decreased from 85.9% of all anticoagulant prescriptions to 42.7%. Conversely, DOAC prescription volume increased from 14.1% of all anticoagulant prescriptions in 2013 to 57.3% in 2018. There were significant differences in prescribing trends based on specialty. Among anticoagulant prescribers prescribing only warfarin in 2018, 1.6% were cardiologists, 12.6% were internal medicine physicians, 20.0% were family medicine physicians and 28.2% were advance practice clinicians.

DOAC availability can improve patients' prior OAC concerns based on when warfarin was the only option. Patients with a needle phobia may now only need annual or bi-annual laboratory testing.[1,3,9] This less frequent lab monitoring may also assist patients with transportation or access concerns.

The largest issue most patients and providers face when considering OAC is cost. DOACs are oftentimes cost prohibitive to patients when directly compared to warfarin. Patients with AF are likely to require indefinite anticoagulation, whereas for initial episodes of VTE, higher drug costs for a fixed 3-to-6-month period may be easier to afford. Furthermore, DOACs are subject to Medicare's coverage gap (i.e. donut hole) as well as annual deductible that make DOAC costs at certain parts of the year much higher than at other times.[50] For example, a DOAC copay may be $480 in January of a calendar year as subject to the deductible, but then as much as 10 times lower (i.e. $47 per month) during the initial coverage phase. The improved bleeding profiles with equal or better efficacy of DOACs are also indirect opportunity costs that are difficult to quantify, particularly for older patients who may experience fixed incomes. Taking into consideration medical bills for lab draws may also improve the conversation when financially comparing OAC options.

Pharmacists have extensive experience with prescription drug coverage/costs in addition to the training and background in pharmacotherapy to differentiate the DOAC drug class from VKAs (Table 1). Manufacturer sponsored copayment assistance cards have improved access to DOACs for many privately insured patients,

FIGURE 4. DOAC PAP Financial Screening Tool*

1. Calculate household size (according to taxes)
2. Approximate gross annual income for household (according to taxes)
3. Gross Income must be ≤ 300% FPL to quality
4. If insured by Medicare Part D, calculate applicant's individual OOP (see below)
5. Submit application for PAP[56-58]

2022 Federal Poverty Level (FPL)	
Household Size	*300%*
1	$40,770
2	$54,930
3	$69,090
4	$83,250
5	$97,410
6	$111,570

**For underinsured or uninsured patients only. Medicare Part D patients are eligible. Wisconsin Medicaid/Badgercare patients are excluded as DOACs are a covered benefit.[59] Patients with commercial insurance programs with high copays should be referred to manufacturer sponsored copay assistance.[51-54]*

Drug PAP	*Program*	*Qualifying Income*	*OOP for Medicare Part D***
Direct Oral Anticoagulants			
ELIQUIS®	BMS	< 300% FPL	3%
PRADAXA®	BOEHRINGER	< 300% FPL	0%
XARELTO®	J & J	< 300% FPL	4%
SAVAYSA®	NO PAP	NO PAP	NO PAP

**OOP = Out of Pocket Spending. OOP is applicable to patients with Medicare Part D coverage only. The OOP is a total percentage of gross income spent in the calendar year on prescription medications for applicant applying for PAP. Patient must submit proof of OOP for PAP sponsored drug to be issued for remainder of calendar year.[56-58]*

but patients who are uninsured or who have coverage under Medicare or Medicaid do not qualify.[51-54] The Janssen Select Program is the only manufacturer sponsored program Medicare Part D patients are eligible for without a financial screening. Janssen Select discounts rivaroxaban for as low as $80 per month to patients with any prescription coverage (including Medicare Part D and any income) from April to December of each calendar year.[55]

Another underutilized financial resource is the availability of manufacturer-sponsored Patient Assistance Programs (PAPs).[56-58] Drug manufacturers offer these programs for patients who are prescribed a DOAC and have a gross income less than 300% the Federal Poverty Level (Figure 4: DOAC PAP Financial Screening Tool). Patients with Medicare Part D coverage wanting access to the PAP for Xarelto® or Eliquis® must meet 3%-4% annual out-of-pocket spending on prescription medications before they will be issued free drug. The PAP applications require both provider and patient signatures and must be submitted annually with proof of income and thus can add complexity and/or additional work to clinical staff.

Conclusion

As pharmacists and healthcare professionals, creating patient relationships allows two-way conversations with shared decision-making of OAC options. While cost can be a common and significant barrier to DOAC use, a deeper dive into financial resources available to patients could improve both overall OAC use as well as facilitate converting patients from a VKA to a DOAC—the preferred anticoagulant for AF and VTE.

Christi Albert, Kristina Yokes, and Anne Rose are Clinical Pharmacists at UW Health Anticoagulation Clinic in Madison, WI.

Disclosure: The author(s) declare no real or potential conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria."

References

1. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society in Collaboration with the Society of Thoracic Surgeons. *Circulation*. 2019;140(2):e125-e151. doi: 10.1161/CIR.0000000000000665
2. Ortel TL, Neumann I, Ageno W, et al. American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. *Blood Adv*. 2020;4(19):4693-4738. doi: 10.1182/bloodadvances.2020001830
3. Stevens SM, Woller SC, Kreuziger LB, et al. Antithrombotic therapy for VTE disease: second update of the CHEST guideline and Expert Panel Report. *Chest.* 2021;160(6):e545-e608. doi: 10.1016/j.chest.2021.07.055
4. COUMADIN® (warfarin sodium) tablets, for oral use. Full prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; 2017.
5. PRADAXA® (dabigatran etexilate mesylate) capsules for oral use. Full prescribing information. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc; 2021.
6. XARELTO® (rivaroxaban) tablets, for oral use. Full prescribing information. Titusville, NJ: Janssen Pharmaceutical, Inc; 2021.
7. ELIQUIS® (apixaban) tablets for oral use. Full prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; 2021.
8. SAVAYSA® (edoxaban) tablets for oral use. Full prescribing information. Parsippany, NJ: Daiichi Sankyo, Inc; 2021.
9. Anticoagulation Forum. Direct Oral Anticoagulant: DOAC Playbook. Updated July 2021. Accessed May 28, 2022. https://acforum-excellence.org/Resource-Center/downloads/DOAC%20Playbook%20_07-2021.pdf
10. Vallakati A, Lewis WR. Underuse of anticoagulation in patients with atrial fibrillation. *Postgrad Med*. 2016;128(2):191-200. doi: 10.1080/00325481.2016.1132939
11. Szucs TD, Bramkamp M. Pharmacoeconomics of anticoagulation therapy for stroke prevention in atrial fibrillation: a review. *J Thromb Haemost.* 2006;4(6):1180-1185. doi: 10.1111/j.1538-7836.2006.01890.x
12. McDermott, A. Types of atrial fibrillation: what you need to know. Healthline. Updated June9th 2020. Accessed June 1, 2022. https://www.healthline.com/health/atrial-fibrillation/types-of-atrial-fibrillation#permanent-afib
13. Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation cohort study. *Eur Heart J*. 2012;33(12):1500-1510. doi: 10.1093/eurheartj/ehr488
14. O'Brien EC, Kim S, Hess PL, et al. Effect of the 2014 atrial fibrillation guideline revisions on the proportion of patients recommended for oral anticoagulation. *JAMA Intern Med.* 2015;175(5):848-850. doi: 10.1001/jamainternmed.2015.13
15. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. *Am J Med*. 2010;123(7):638-645. doi: 10.1016/j.amjmed.2009.11.025
16. Baczek VL, Chen WT, Kluger J, Coleman CI. Predictors of warfarin use in atrial fibrillation in the United States: a systematic review and meta-analysis. *BMC Fam Pract.* 2012;13:5. doi: 10.1186/1471-2296-13-5
17. Shoeb M, Fang MC. Assessing bleeding risk in patients taking anticoagulants. *J Thromb Thrombolysis.* 2013;35(3):312-319. doi: 10.1007/s11239-013-0899-7
18. Fang MC, Go AS, Chang Y, et al. Warfarin discontinuation after starting warfarin for atrial fibrillation (ATRIA). *Circ Cardiovasc Qual Outcomes*. 2010;3(6):624-631. doi: 10.1161/CIRCOUTCOMES.110.937680
19. O'Brien EC, Simon DN, Allen LA, et al. Reasons for warfarin discontinuation in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF). *Am Heart J.* 2014;168(4):487-494. doi: 10.1016/j.ahj.2014.07.002
20. Piccini JP, Xu H, Cox M, et al. Adherence to guideline-directed stroke prevention therapy for atrial fibrillation is achievable. *Circulation.* 2019;139(12):1497-1506. doi: 10.1161/CIRCULATIONAHA.118.035909
21. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992. doi: 10.1056/NEJMoa1107039
22. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369(22):2093-2104. doi: 10.1056/NEJMoa1310907
23. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2009;361(12):1139-1151. doi: 10.1056/NEJMoa0905561
24. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation (ROCKET-AF). *N Engl J Med.* 2011;365(10):883-891. doi: 10.1056/NEJMoa1009638
25. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med.* 2013;369(13):1206-1214. doi: 10.1056/NEJMoa1300615
26. Siontis KC, Zhang X, Eckard A, et al. Outcomes Associated with Apixaban Use in Patients with End-Stage Kidney Disease and Atrial Fibrillation in the United States *Circulation*. 2018;138(15):1519-1529. doi: 10.1161/CIRCULATIONAHA.118.035418
27. Wang X, Tirucherai G, Marbury TC, et al. Pharmacokinetics, pharmacodynamics, and safety of apixaban in subjects with end-stage renal disease on hemodialysis. *J Clin Pharmacol.* 2016;56(5):628-636. doi: 10.1002/jcph.628
28. Hylek EM. Apixaban for End-Stage Kidney Disease. *Circulation.* 2018;138(15):1534-1536. doi: 10.1161/CIRCULATIONAHA.118.036449
29. Kubitza D, Becka M, Mueck W, et al. Effects of renal impairment on the pharmacokinetics, pharmacodynamics and safety of rivaroxaban, an oral, direct Factor Xa inhibitor. *Br J Clin Pharmacol*. 2010;70(5):703-712. doi: 10.1111/j.1365-2125.2010.03753.x
30. Lip GYH, Keshishian A, Li X, et al. Effectiveness and Safety of Oral Anticoagulants Among Nonvalvular Atrial Fibrillation Patients. *Stroke*. 2018;49(12):2933-2944. doi: 10.1161/STROKEAHA.118.020232
31. Comparison of Efficacy and Safety Among Dabigatran, Rivaroxaban, and Apixaban in Non-Valvular Atrial Fibrillation (DARING-

AF). ClinicalTrials.gov. Updated February 17th 2016. Accessed June 1st 2022. https://clinicaltrials.gov/ct2/show/NCT02666157
32. The Danish Non-vitamin K Antagonist Orla Anticoagulation Study in Patients with Atrial Fibrillation (DANNOAC-AF). Updated August 7th 2018. Accessed June 1st 2022. https://clinicaltrials.gov/ct2/show/NCT03129490
33. Venous Thromboembolism (Blood Clots). Centers for Disease Control and Prevention. Updated April 25, 2022. Accessed May 28, 2022. https://www.cdc.gov/ncbddd/dvt/data.html
34. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510. doi: 10.1056/NEJMoa1007903
35. EINSTEIN–PE Investigators, Büller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med*. 2012;366(14):1287-1297. doi: 10.1056/NEJMoa1113572
36. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808. doi: 10.1056/NEJMoa1302507
37. Hokusai-VTE Investigators, Büller HR, Décousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism [published correction appears in *N Engl J Med.* 2014 Jan 23;370(4):390]. N Engl J Med. 2013;369(15):1406-1415. doi: 10.1056/NEJMoa1306638
38. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361(24):2342-2352. doi: 10.1056/NEJMoa0906598
39. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation*. 2014;129(7):764-772. doi: 10.1161/CIRCULATIONAHA.113.004450
40. Khan F, Rahman A, Carrier M, et al. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. *BMJ*. 2019;366:l4363. doi: 10.1136/bmj.l4363
41. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368(8):699-708. doi: 10.1056/NEJMoa1207541
42. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med.* 2013;368(8):709-718. doi:10.1056/NEJMoa1113697
43. EINSTEIN Investigators, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med*. 2010;363(26):2499-2510. doi:10.1056/NEJMoa1007903
44. Weitz JI, Lensing AWA, Prins MH, et al. Rivaroxaban or aspirin for extended treatment of venous thromboembolism. *N Engl J Med*. 2017;376(13):1211-1222. doi: 10.1056/NEJMoa1700518
45. REduced Dose Versus Full-dose of Direct Oral Anticoagulant After uNprOvoked Venous thromboembolism (RENOVE). ClinicalTrials.gov. Updated April 22, 2022. Accessed May 28, 2022. https://clinicaltrials.gov/ct2/show/NCT03285438
46. Frost H, Campbell P, Maxwell M, et al. Effectiveness of motivational interviewing on adult behavior change in health and social care settings: a systematic review of reviews. *PLoS One*. 2018;13(10):e0204890. doi: 10.1371/journal.pone.0204890
47. Bradshaw J, Siddiqui N, Greenfield D, Sharma A. Kindness, listening, and connection: patient and clinician key requirements for emotional support in chronic and complex care. *J Patient Exp*. 2022;9:1-7. doi: 10.1177/23743735221092627
48. Barnes GD, Acosta J, Graves C, et al. Barriers to integrating direct oral anticoagulants into anticoagulation clinic care: a mixed-methods study. Res Pract Thromb Haemost. 2018;3(1):79-84. doi: 10.1002/rth2.12157
49. Wheelock KM, Ross JS, Murugiah K, Lin Z, Krumholz HM, Khera R. clinician trends in prescribing direct oral anticoagulants for US Medicare beneficiaries. *JAMA Netw Open.* 2021;4(12):e2137288. doi: 10.1001/jamanetworkopen.2021.37288
50. Pharmacist Quick 2022 Medicare Part D Reference. National Community Pharmacists Association (NCPA) Guide. Accessed June 1, 2022. https://ncpa.org/sites/default/files/2021-10/quick-ref-guide-medicare-part-d-2022.pdf
51. Eliquis® 360 Support. Bristol-Myers Squibb Company. Updated 2021. Accessed June 1, 2022 Savings And Support | Rx ELIQUIS® (apixaban) (bmscustomerconnect.com)
52. Janssen CarePath Trial Offer Card for Xarelto®. Janssen Pharmaceuticals, Inc. Updated December 2021. Accessed June 1, 2022. Trial Offer Card - XARELTO (trialcard.com)
53. Janssen CarePath Savings Program $10 Copay Card for Xarelto®. Janssen Pharmaceuticals, Inc. Updated March 2022. Accessed June 1, 2022. Savings Program Overview – XARELTO (janssencarepath.com)
54. Savaysa Support. Daiichi Sankyo, Inc. Updated August 2020. Accessed June 1, 2022. Support+™ Program & Resources | SAVAYSA® (edoxaban)
55. Janssen Select Affordability Program for Xarelto®. Janssen Pharmaceuticals, Inc. Updated March 2022. Accessed June 1, 2022. Janssen Select Affordability Program for XARELTO® (rivaroxaban)
56. Bristol Myers Squibb Patient Assistance Foundation (BMSPAF) Eliquis® Application. Updated August 2021. Accessed June 1, 2022. https://www.needymeds.org/papforms/bmspae0042.pdf
57. Johnson & Johnson Foundation, Inc. Xarelto® Patient Assistance Program Application. Updated January 2022. Accessed June 1, 2022. https://www.needymeds.org/papforms/jpapae0996.pdf
58. Boehringer Ingelheim Cares Foundation. Patient Assistance Program Application. Updated May 17th 2022. Accessed June 1, 2022. https://www.needymeds.org/papforms/bicpae3360.pdf
59. Wisconsin Medicaid Preferred Drug List Quick Reference. Forward Health, Wisconsin Serving You. Updated June 1st 2022. Accessed June 1, 2022. https://www.forwardhealth.wi.gov/wiportal/content/provider/medicaid/pharmacy/resources.htm.spage#

Assessment Questions

1. When selecting an oral anticoagulant for a patient, which of the following should NOT be taken into consideration?
   a. Medication copay
   b. Renal function
   c. Reversal agents
   d. Drug interactions

2. DOACs have which of the following advantages over VKAs?
   a. Limited dietary interactions
   b. Preferred anticoagulant for AF and VTE
   c. Rapid onset
   d. All of the above

3. Which is NOT a contraindication for use of a DOAC?
   a. Triple positive antiphospholipid antibody syndrome
   b. Creatinine clearance of 20 mL/min
   c. Mechanical heart valve replacement
   d. Concurrent use of rifampin

4. **True or False:** DOACs can be used in patients with mechanical heart valves or moderate to severe mitral stenosis as long as they have underlying atrial fibrillation.
   a. True
   b. False

5. **True or False:** Edoxaban (Savaysa®) would be a reasonable DOAC to continue for a patient with AF while hospitalized with anuric AKI requiring dialysis if they had been established on it as an outpatient before hospital admission.
   a. True
   b. False

6. **True or False:** A patient with AF should not take oral anticoagulation if a prescriber has not documented the CHA2DSVASC2 score in the medical record.
   a. True
   b. False

7. In a patient with a new PE, which anticoagulant can be used for initial treatment without low molecular weight heparin (LMWH)?
   a. Warfarin
   b. Dabigatran
   c. Edoxaban
   d. Apixaban

8. Which DOAC is NOT approved for extended treatment of VTE?
   a. Apixaban
   b. Dabigatran
   c. Edoxaban
   d. Rivaroxaban

9. A patient with Medicare Part D has an annual income of $42,000 with a

household size of two people. She has currently spent 3% of her income on out-of-pocket Medicare Part D expenses. Which medication's PAP programs could she apply for?
a. Eliquis® and Pradaxa®
b. Eliquis® and Xarelto®
c. Xarelto® and Pradaxa®
d. Pradaxa® and Xarelto®

10. A thirty-year old patient is diagnosed with a new DVT. He has commercial drug insurance with a tier 2 DOAC copay of $50/month. What resource would likely provide him cost savings?
a. Manufacturer patient assistance programs
b. Manufacturer copay cards
c. Switching pharmacies
d. Discount prescription drug cards

11. Did the activity meet the stated learning objectives? (if you answer no, please email sarahs@pswi.org to explain)
a. Yes
b. No

12. On a scale of 1 – 10 (1-no impact; 10-strong impact), please rate how this program will impact the medication therapy management outcomes or safety of your patients.

13. On a scale of 1 – 10 (1-did not enhance; 10-greatly enhanced), please rate how this program enhanced your competence in the clinical areas covered.

14. On a scale of 1 – 10 (1-did not help; 10-great help), please rate how this program helped to build your management and leadership skills.

15. How useful was the educational material?
a. Very useful
b. Somewhat useful
c. Not useful

16. How effective were the learning methods used for this activity?
a. Very effective
b. Somewhat effective
c. Not effective

17. Learning assessment questions were appropriate.
a. Yes
b. No

18. Were the authors free from bias?
a. Yes
b. No

19. If you answered "no" to question 18, please comment (email info@pswi.org).

20. Please indicate the amount of time it took you to read the article and complete the assessment questions.

CE FOR **PHARMACISTS**

Submit Your CE Online!

www.pswi.org/Education/Journal-CE

Continuing Education Credit Information

The Pharmacy Society of Wisconsin is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. Continuing education credit can be earned by completing the self assessment questions. Questions may be completed online at www.pswi.org or by mailing completed answer form to PSW, 701 Heartland Trail, Madison, WI 53717. Participants receiving a score of 70% or better will be granted 1hour (0.1 CEU) credit through CPE Monitor within 60 day of quiz completion. Accurate birth date (MMDD) and CPE Monitor ID must be provided in order to receive this credit as required by ACPE.

This CE offering is offered free-of-charge to all PSW members. Nonmembers are charged $20 for each exam submitted to cover administrative costs.

Quiz Answer Form

circle one answer per question

1) a b c d
2) a b c d
3) a b
4) a b
5) a b
6) a b
7) a b c d
8) a b c d
9) a b c d
10) a b c d
11) a b
12)_____
13)_____
14)_____
15) a b c
16) a b c
17) a b
18) a b
19)_____
20)_____

July/August 2022
The X-Factor: Overcoming DOAC Barriers in OAC Eligible Patients

ACPE Universal Activity Number: 0175-0000-22-108-H04-P

Target Audience: Pharmacists
Activity Type: Knowledge-based
Release Date: July 1, 2022
(No longer valid for CE credit after July 1, 2025)

Name_____ Designation (RPh, PharmD, etc.) _____

CPE Monitor # _____ DOB (MMDDYY) _____

Preferred Mailing Address_____

City _____ State_____ Zip _____

Is this your home ☐ or work ☐ address?