Oral Anticoagulants: Direct-Acting Oral Anticoagulants and Vitamin K Antagonists

Executive Summary

- **For the MTF Formulary Management Document with the formulary recommendation from the November 2016 P&T Committee meeting, see http://www.health.mil/DoDPTResources.**
- The branded direct-acting oral anticoagulants (DOACs) dabigatran (Pradaxa), rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) provide additional options to warfarin for treating patients with non-valvular atrial fibrillation (NVAF), venous thromboembolism (VTE) including pulmonary embolism or deep venous thrombosis, or for VTE prophylaxis following hip and knee replacement surgeries.
- The majority of patients in the Military Health System are receiving a DOAC for the prevention of stroke and systemic embolism in atrial fibrillation.
- The DOACs offer a convenience to patients in that laboratory monitoring for efficacy and dietary restrictions are not required. Additional data with the products is needed in patients with renal or hepatic impairment to more fully characterize the risk-to-benefit ratio.
- Since the most recent DoD P&T Committee review in May 2015, there are no major clinical updates for the oral anticoagulants, with the exception that dabigatran is now approved for prevention of VTE following total hip replacement (THR) in a new 110 mg capsule formulation.
- Idarucizumab (Praxbind) is an injectable reversal agent for dabigatran that received FDA approval in October 2015. A reversal agent for the factor Xa inhibitors, andexanet alfa, is under investigation, but whether and when it will reach the market is undetermined.
- While the DOACs have some advantages over warfarin, knowledge of their differences in dosing, in particular alternative dosing regimens for special populations, and clinical trial data is essential when selecting the most appropriate patients. Warfarin remains a viable option due to the large clinical data available, particularly in patients with mechanical heart valves and patients with renal dysfunction.

Background and Prior P&T Committee Actions

- There are currently five products in the class, the vitamin K antagonist warfarin (Coumadin), and four direct-acting oral anticoagulants (DOACs). The DOACs are further classified as direct thrombin inhibitors [dabigatran (Pradaxa)], and the factor Xa inhibitors [rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa)]. (See Table 1 for the drugs in the class.)
- The terminology for the non-vitamin K products includes “newer oral anticoagulants” (NOACs) or “targeted-specific oral anticoagulants” (TSOACs), in addition to “DOACs”.

Table 1: Oral Anticoagulants Available in the United States[1-4]

Generic Name	Brand Name Manufacturer	Formulations	FDA Approval Date	Patent Expiration Date
Vitamin K Antagonists				
Warfarin	Coumadin (generic)	1, 2, 2.5, 3, 4, 5, 6, 7.5, & 10 mg tabs	06/08/1954	Expired
Direct Thrombin Inhibitors				
dabigatran	Pradaxa (Boehringer Ingelheim)	75, 110, & 150 mg capsules	10/19/2010	2018-2027
Factor Xa Inhibitors				
rivaroxaban	Xarelto (J&J)	10, 15, & 20 mg tabs	07/01/2011	2020-2021
	Eliquis (BMS/Pfizer)	2.5 & 5 mg tabs	12/28/2012	2019-2023
edoxaban	Savaysa (Daiichi Sankyo)	15, 30, 60 mg tabs	01/08/2015	2021-2024

- **Previous Uniform Formulary (UF) Reviews:** The oral anticoagulants were previously reviewed in February 2013, May 2014 (with apixaban reviewed as newly-approved drug), and May 2015. Currently, warfarin is the sole product included on the Basic Core Formulary (BCF), and dabigatran, rivaroxaban, apixaban, and edoxaban are designated as UF. The selection of warfarin for BCF status dates back to 1998, before implementation of the UF Rule; warfarin was then maintained on the BCF with the reviews in 2013 and 2015.

- **November 2016 Review:** The DOAC class was selected for re-review, with the goal of considering BCF status for one of the branded products, in addition to warfarin.
- **Mechanism of Action:** Warfarin has a complex mechanism of action, and inhibits the activation of the vitamin K dependent clot factors II, VII, IX, X, and protein C and S, which are all essential precursors to thrombus formation. In contrast, the DOACs target only one part of the clotting cascade. Thrombin is the final step in coagulation cascade and inhibition of thrombin prevents the conversion of fibrinogen to the stable fibrin clot and also prevents further generation of thrombin. The direct thrombin inhibitors (dabigatran) can inactivate fibrin-bound thrombin (fibrin-bound thrombin triggers expansion of the thrombus) and free thrombin equally well. The factor Xa inhibitors (apixaban, dabigatran, rivaroxaban) work earlier up in the clotting cascade and inhibit thrombus formation by preventing the ability of factor Xa to convert prothrombin to thrombin.
- **DOACs versus Warfarin:** Compared to warfarin, the direct thrombin inhibitors and factor Xa inhibitors have advantages of predictable anticoagulant effect, fixed dosing, fast onset of action, fewer drug interactions, and no dietary restrictions. Advantages of warfarin include its long history of use, greater number of FDA-approved indications, ability to monitor for efficacy, safety and adherence with the International Normalized Ratio (INR), and the availability of a reliable reversal agent (vitamin K and fresh frozen plasma).
- **FDA-Approved Indications:** Table 2 shows the FDA indications for the oral anticoagulants and the low-molecular weight heparin (LMWH) enoxaparin (Lovenox). Warfarin has the greatest number of indications, including in patients with mechanical cardiac valves and following myocardial infarction. All the DOACs are indicated for prevention of stroke and systemic embolism in NVAF, while warfarin can also be used in patients with atrial fibrillation and valvular heart disease. All the DOACs are approved for the acute treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE), while only dabigatran, rivaroxaban, and apixaban can be used for extended VTE treatment. For acute treatment of VTE, dabigatran and edoxaban require overlap with LMWH for 5-10 days, due to the study design for the individual trials.
- **Off-label Uses:** Clinical trials for several other conditions are underway for the DOACs, including as a bridge to direct current cardioversion or catheter ablation, for DVT prophylaxis in medially ill patients, for acute VTE treatment or prevention in patients with cancer, and for patients undergoing percutaneous coronary intervention. Some smaller studies are examining treatment in the pediatric population.

Table 2: FDA Indications for the Oral Anticoagulants and FDA Approval Dates[1-4]

Indication	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban	Enoxaparin
Stroke prevention in NVAF	**X**	**X** **Oct 2010**	**X** **Nov 2011**	**X** **Dec 2011**	**X** **Jan 2015**	
Stroke prevention for mechanical cardiac valves	**X**					
VTE prophylaxis after THR or TKR	**X**	THR only Nov 2015	X (Jul 2011)	X (Mar 2014)		*X
VTE prophylaxis after hip fracture	**X**					
Acute VTE treatment DVT and PE	**X**	X (Apr 2014) +LMWH 5-10d	X (Nov 2012)	X (Aug 2014)	X (Jan 2015) +LMWH 5-10d	X DVT: out-pt PE: in-pt only
↓ risk of recurrent PE/DVT (Extended VTE Treatment)	**X**	X (Apr 2014)	X (Nov 2012)	X (Aug 2014)		
↓ death/recurrent MI/stroke post MI	**X**					

* enoxaparin also approved for VTE prophylaxis in medically ill patients for general surgery (abdominal); also has additional cardiac indications

DVT: deep venous thrombosis; in-pt: inpatient; LMWH: low molecular weight heparin; MI: myocardial infarction; NVAF: non- valvular atrial fibrillation; out-pt: outpatient; PE: pulmonary embolism; VTE: venous thromboembolism; THR: total hip replacement; TKR: total knee replacement

- **Pharmacokinetics:** Compared with warfarin, the DOACs have a quick onset of action and short duration of action, with half-lives averaging about 12 hours. The half-life of warfarin is dependent on the vitamin K clotting factors, with 40 hours as the average time; the full therapeutic effect is usually seen within five to seven days. Renal clearance plays a major role for

the elimination of dabigatran, accounting for 80% of its clearance. Rivaroxaban (66% renal clearance), edoxaban (50% renal clearance), and apixaban (27% renal clearance) depend on renal elimination to a lesser extent than dabigatran. Patients with impaired renal function can significantly accumulate the DOACs, leading to increased risk of bleeding. Apixaban also requires twice daily dosing in the treatment of NVAF, even though the half-lives of the DOACs are similar.

- **Dosing:** For warfarin, depending on the indication, doses are individualized to maintain INRs in the target range, most commonly 2-3. For the DOACs, dosing varies by indication, and often by degree of renal impairment, or body weight and age. In patients with NVAF, rivaroxaban and edoxaban are dosed once daily, with dabigatran and apixaban requiring twice daily dosing. Rivaroxaban doses greater than 10 mg require administration with the evening meal; dabigatran, apixaban, and edoxaban can be taken without regard to meals. Table 3 contains the dosing recommendations for the DOACs; note that dosing for the alternative regimens for NVAF patients is based only on limited data. For edoxaban, renal function is particularly important in that the package insert states the patients with CrCl >95 mL/min should not receive the drug for NVAF, as the risk of stroke or systemic embolism was increased in this particular subgroup.

Table 3: FDA Dosing—Direct-Acting Oral Anticoagulants[1-5]

Indication	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
NVAF	CrCl > 30 mL/min 150 mg BID	CrCl > 50 mL/min 20 mg QD food	5 mg BID	CrCl between >50 mL/min and ≤ 95mL/min 60 mg QD
NVAF* alternate dosing	CrCl 15-30 mL/min 75 mg BID CrCl <15 mL/min or dialysis: no dosing recommendations	CrCl 15-50 mL/min 15 mg QD food CrCl<15 mL/min: avoid	2.5 mg BID if two of the following factors: age ≥80 yrs, weight ≤60 kg SCr ≥1.5 mg/dL	CrCl 15-50 mL/min 30 mg QD CrCL < 15 mL/min: use not recommended CrCl >95 mL/min: use not recommended
VTE prophylaxis THR	CrCl >30 mL/min 110 mg day #1, then 220 mg QD (Nov 2015)	10 mg QD x 35 days	2.5 mg BID x 35 days	Not approved
VTE prophylaxis TKR	Not approved	10 mg QD x 12 days	2.5 mg BID x 12 days	Not approved
VTE Treatment	Acute & Extended: CrCL>30 mL/min 150 mg BID after LMWH or UFH x 5-10 days	Acute & Extended: CrCl >30 mL/min 15 mg BID x 21 days, then 20 mg QD food	Acute: 10 mg BID x 7 days, then 5 mg BID Extended: 2.5 mg BID	60mg QD after LMWH of UFH for 5-10 days 30mg QD if: CrCl 15-50 mL/min or weight ≤ 60 kg or drug interactions

* Alternate dosing regimen notes:

- Dabigatran: 75 mg dose never studied clinically; FDA approval was based on a pharmacokinetic trial; no pts studied with CrCl <30 mL/min in the RELY trial
- Rivaroxaban: 8 pts had CrCl <30 mL/min in ROCKET-AF trial
- Apixaban: no data in pts with CrCl of 15-30 mL/min from the ARISTOTLE trial
- Edoxaban: Doses of 75-90 mg may have improved efficacy with acceptable safety in patients with CrCl ≥80. Do not use if CrCl > 95 mL/min, based on the ENGAGE trial.

Guidelines

Non-valvular Atrial Fibrillation (NVAF)

- Treatment guidelines from the American College of Cardiology/American Heart Association/Heart Rhythm Society (2014) do not provide a preference for one DOAC over another. Warfarin is designated as having an evidence rating of level A, with data available from multiple clinical trials, while the DOACs are rated with evidence level B, with data based on a single trial for each drug. The guidelines do state that patients taking warfarin who have stable INRs and are satisfied with vitamin K antagonist therapy can remain on warfarin.[6]
- The American Academy of Neurology (2014) guidelines conclude that apixaban, dabigatran, and rivaroxaban are at least as effective as warfarin in preventing stroke and have a lower risk of intracranial hemorrhage. Edoxaban is not mentioned since it was not FDA-approved at the time of guideline publication.[7]
- The American College of Chest Physicians (CHEST) have not yet updated their recommendations from 2012 regarding use of the DOACs for stroke prevention in NVAF.[8]

Venous Thromboembolism (VTE)

- The CHEST guidelines were updated in February 2016. In patients with VTE without cancer, all four DOACs are given a class 2B (grade 2 = weak; B = moderate quality evidence) recommendation over warfarin for treatment of DVT or PE, while warfarin is given a class 2C (low quality evidence) recommendation over LMWH. In contrast, in patients with VTE and underlying cancer, LMWH is given a class 2B recommendation over warfarin, and LMWH is given a class 2C recommendation over the DOACs.[19]

VTE Prophylaxis following Orthopedic Surgery (Hip or Knee Replacement)

- The CHEST guidelines from 2012 have not been updated to reflect recommendations for all four of the DOACs. When an update might occur is unknown at this time.

Efficacy

Non-valvular Atrial Fibrillation (NVAF)

- There are no head-to-head trials comparing one DOAC versus another DOAC for stroke prevention in NVAF. The DOACs were each compared with adjusted-dose warfarin in four large, non-inferiority clinical trials in patients with NVAF: apixaban (ARISTOTLE), dabigatran (RELY), edoxaban (ENGAGE), and rivaroxaban (ROCKET-AF). These trials enrolled patients with varying degrees of stroke risk in atrial fibrillation, based on the CHADS2 score; bleeding endpoints also differed. A brief description of the trials follows below, and a summary of the study statistical results is found in Table 4.
    - **Dabigatran (RE-LY):** Dabigatran at a dosage of 150 mg BID significantly reduced the primary composite endpoint of stroke and systemic embolism (2.2%) versus warfarin (3.4%). Dabigatran was superior in reducing ischemic and hemorrhagic strokes. The median follow-up was two years. Dabigatran and warfarin had similar rates of major bleeds in this trial; however, dabigatran was associated with a higher rate of GI bleeding.[10]
    - **Rivaroxaban (ROCKET AF):** Rivaroxaban was non-inferior to warfarin for the primary composite endpoint of time to first stroke or non-central nervous system embolism (3.8% versus 4.3%); superiority to warfarin was not noted. The median follow-up was 590 days. Rivaroxaban and warfarin had a similar incidence of major bleeding; however, rivaroxaban had a lower rate of fatal bleeding.[11]
    - **Apixaban (ARISTOTLE):** Apixaban was superior to warfarin in reducing the primary endpoint of the risk of stroke and systemic embolism (n = 212 events with apixaban [1.27% per year] versus 265 events with warfarin [1.60% per year]) [P = 0.01]. The superiority was mainly due to a reduction in hemorrhagic stroke. Apixaban also was associated with a lower rate of all-cause death compared with warfarin (P = 0.046). Patients were followed for a median of 89 weeks. Treatment with apixaban led to significantly fewer major bleeds compared with warfarin.[12]
    - **Edoxaban (ENGAGE AF-TIMI 48)**: Edoxaban was non-inferior to warfarin for the occurrence of first stroke or of a systemic embolic event (1.2% per year with edoxaban 60 mg QD versus 1.5% per year with warfarin). Treatment was for a median of 2.5 years. Major bleeding occurred less frequently with edoxaban than with warfarin. Patients receiving 60 mg edoxaban who had CrCl above 95 mL/min surprisingly had a higher risk of stroke than patients with lower CrCl rates; the drug is therefore not approved for use in this specific patient population.[13]

Table 4: Summary of the NVAF trials of DOACs versus Warfarin*[14]

Parameter	RE-LY Dabigatran	ROCKET AF Rivaroxaban	ARISTOTLE Apixaban	ENGAGE AF TIMI 48 Edoxaban
Study Design all were non-inferiority	PROBE (Prospective Randomized Open Blinded Endpoint)	Double-blind, double-dummy	Double-blind, double dummy	Double-blind, double-dummy
Inclusion	NVAF + ≥1 additional stroke risk factor	NFAF + ≥3 additional stroke risk factors or previous thromboembolism	NFAF + ≥1 additional stroke risk factor	NVAF + $CHADS_2$ ≥2
CHADS2 score	2.1	3.46	2.1	2.8
N	18,113	14,264	18,201	21,2015
Dosing	Dabigatran 150 mg BID (Dabigatran 110 mg BID results not given)	Rivaroxaban 20 mg QD	Apixaban 5 mg QD	Edoxaban 60 mg QD (Edoxaban 30 mg QD results not given)
Warfarin Time in Therapeutic Range	TTR=67%	TTR=58%	TTR=66%	TTR=68.4%
Primary Endpoint	Reduction in stroke or systemic embolism at 2.8 yrs	Reduction in stroke or systemic embolism at 2 yrs	Reduction in stroke or systemic embolism at 1.6 yrs	Reduction in stroke or systemic embolism at 1.8 yrs
Major Safety Endpoint	Major bleeding	Major bleeding and clinical relevant bleeding	Major bleeding	Major bleeding
Reduction in Stroke/Systemic Embolism	0.65 (0.52-0.81) Superior	0.88 (0.74-1.03) Non-Inferior	0.79 (0.66-0.95) Superior	0.87 (0.73-1.04) Non-Inferior
Reduction in Ischemic Stroke	0.76 (0.60-0.99) ↓	0.94 (0.75-1.17)	1.02 (0.81-1.29)	1.00 (0.83–1.19)
Intracranial Hemorrhage	0.40 (0.27-0.60) ↓	0.67 (0.47-0.94) ↓	0.42 (0.30-0.58) ↓	0.47 (0.34-0.63) ↓
All-Cause Mortality	0.88 (0.77-1.00)	0.85 (0.79-1.02)	0.89 (0.80-0.998) ↓	0.92 (0.83-1.01)
Major Bleeding	0.93 (0.81-1.07)	1.04 (0.90-1.20)	0.69 (0.60-0.80) ↓	0.80 (0.71-0.91) ↓
GI Bleeding	1.50 (1.19-1.89) ↑	3.15 (Confidence interval not reported) ↑	0.89 (0.70-1.15)	1.23 (1.02-1.50) ↑

* All results given as a hazard ratio with a 95% confidence interval of the DOAC versus warfarin.

Downward pointing arrows denote statistically significant difference in favor of DOAC versus warfarin.

Upward pointing red arrows denote statistically significant increased risk with DOAC.

Adapted from Garwood CL. American College of Clinical Pharmacy 2014;55-106.

- In patients with NVAF, the DOACs are at least as effective as warfarin in preventing stroke, are easier to use, and have a lower risk of intracranial hemorrhage.
- In NVAF, dabigatran and apixaban were superior to not optimally controlled warfarin at preventing stroke and systemic embolism, including hemorrhagic stroke, while edoxaban and rivaroxaban were non-inferior to warfarin for these outcomes.
- Intracranial bleeding was lower with all four DOACs compared with warfarin in the major trials used to obtain FDA approval.
- Edoxaban advantages include once daily dosing and an overall lower rate of bleeding versus warfarin. Disadvantages include a higher rate of gastrointestinal (GI) bleeding, and a higher risk of stroke in patients with creatinine clearance greater than 95 mL/min.
- Dabigatran was the only DOAC to show superior ischemic stroke reduction, but it has a higher incidence of GI bleeding than warfarin, causes dyspepsia, and is highly dependent on renal clearance.

- Rivaroxaban advantages include once daily dosing, but it has an increased incidence of GI bleeding and major bleeding compared to warfarin. The patient population studied with rivaroxaban had more comorbidities than the other three DOACs.
- Apixaban had significantly less major bleeding than warfarin, and was the only DOAC to show a reduction in mortality, but the confidence interval approached one. The point estimates and confidence intervals for all the DOACs are similar for mortality.

Venous Thromboembolism (VTE)[15-18]

- All four DOACs are indicated for the acute treatment of PE and DVT. In contrast to the other DOACs, edoxaban does not have an indication for extended treatment of VTE to prevent recurrent PE/DVT. In the HOKUSAI VTE trial used to obtain FDA approval for edoxaban for this indication, all endpoints were measured at 12 months, regardless of the amount of time the patient was enrolled in the trial. This study design is different from the other trials, where the events were measured when they actually occurred. Edoxaban is unlikely to be approved for extended treatment of VTE due to this study design difference. Table 5 contains a brief summary of the major trials used to obtain FDA approval for acute VTE treatment.
- Apixaban and rivaroxaban do not require overlap with LMHW for acute treatment of VTE, while dabigatran and edoxaban do require overlap with LMWH.
- All four DOACs were non-inferior to LMWH and/or warfarin for the composite endpoint of recurrent VTE, nonfatal PE, or death.
- Apixaban and rivaroxaban had significantly less major bleeding than LMWH and/or warfarin, while there was no significant difference in major bleeding with edoxaban or dabigatran versus warfarin.

Table 5: Summary of the Acute VTE trials of DOACs versus Standard of Care*[14]

Parameter	HOKUSAI VTE Edoxaban	RECOVER Dabigatran	AMPLIFY Apixaban	EINSTEIN-DVT Rivaroxaban	EINSTEIN-DVT Rivaroxaban
N	8,240	5,107	5,395	8,282 (pooled)	8,282 (pooled)
Design	Double blind	Double blind	Double blind	Open label	Open label
LMWH Overlap / Dosing	YES then 60 mg QD	YES then 150 mg BID	No 10 mg BID x 7 days then 5 mg BID	No 15 mg BID x 21 days then 20 mg QD	No 15 mg BID x 21 days then 20 mg QD
Comparator	Parenteral Anticoagulation (UFH, LMWH, or fondaparinux) then bridge to VKA				
Duration of Therapy	12 months after treatment initiation, regardless of time on treatment	6 months	6 months	3, 6, or 12 months	3, 6, or 12 months
VTE Recurrence or death	0.89 (0.70-1.13) **Non-Inferior** PE with RV dysfunction Superior	0.98 (0.53-1.79) **Non-Inferior**	0.84 (0.60-1.18) **Non-Inferior**	0.68 (0.44-1.04) **Non-Inferior**	1.12 (0.75 -1.68) **Non-Inferior**
Major Bleeding	0.84 (0.59-1.21)	0.82 (0.45-1.48)	0.31 (0.17-0.55) ↓	0.65 (0.33-1.30)	0.49 (0.31- 0.79) ↓

* All results given as a hazard ratio with a 95% confidence interval of the DOAC versus comparator.

Downward pointing arrows denote statistically significant difference in favor of DOAC versus comparator.

Upward pointing red arrows denote statistically significant increased risk with DOAC.

Adapted from Garwood CL. American College of Clinical Pharmacy 2014;55-106.

VTE Prophylaxis following Orthopedic Surgery (Hip or Knee Replacement)

- The DOACs offer a convenience to patients in that LMWH injections are not required.
- Rivaroxaban and apixaban are FDA-approved for prophylaxis of VTE following both hip and knee replacement surgery, while edoxaban is not approved.
- Since the May 2015 P&T Committee review, dabigatran received FDA-approval for VTE prophylaxis following THR, based on the results of the RENOVATE I and RENOVATE II trials, which included 5,248 patients with a mean age of 63 years. The treatment included dabigatran 220 mg QD versus enoxaparin 40 mg QD. The primary endpoint was a composite of confirmed VTE and all-cause death; overall, dabigatran was non-inferior to enoxaparin. In RENOVATE I, the primary endpoint occurred with an incidence of 6% with dabigatran versus 6.7% with enoxaparin, for a risk difference -0.7% (95% confidence interval -2.9 to 1.6). In RENOVATE II, the results for the primary endpoint were dabigatran 7.7% versus enoxaparin 8.8%, with a risk difference of -1.1% (95% CI -3.8 to 1.6). For major bleeding, the results showed either no difference or an increased rate with enoxaparin.[19-20] A new capsule formulation of 110 mg was approved for this indication in November 2015.

Reversal Agents

- **Direct Thrombin Inhibitors**
  - Since the last DoD P&T Committee review in May 2015, a reversal agent for dabigatran received FDA approval in November 2015. **Idarucizumab (Praxbind, Boehringer Ingelheim)** is indicated when reversal is required. The product is a humanized monoclonal antibody fragment (Fab) that binds to dabigatran and metabolites with a 350 times higher affinity than that of dabigatran to thrombin. As a result, the anticoagulant effect of dabigatran is neutralized. Idarucizumab binds free and thrombin-bound dabigatran and neutralizes its activity.
  - Idarucizumab is a solution which is given as IV push; the dose administered is 5 grams (2.5 grams given in two doses). Initial clinical trial results from the REVERSE-AD trial conducted in patients receiving dabigatran who were actively bleeding or required emergent surgery were used to obtain FDA approval. The primary endpoint was change in laboratory tests of anticoagulation, but clinical outcomes were reported. From the 90 patients included in the publication, 36 patients underwent urgent procedures, and normal intraoperative hemostasis was attained in 92% of cases. The median time to bleeding cessation was 11.4 hours. The FDA is gathering additional data from idarucizumab looking at outcomes of bleeding.[21]
- **Factor Xa Inhibitors**
  - **Andexanet Alfa (Portola Pharmaceuticals**) is under investigation as a reversal agent for the factor Xa inhibitors. This product is a recombinant, inactive factor Xa "decoy," which binds the Xa inhibitor drugs similarly as with binding to native factor Xa. Andexanet alfa will bind factor Xa inhibitors, but does not have intrinsic catalytic activity.
  - Preliminary results from the ANNEXA-4 open-label trial in 67 patients with acute active bleeding were published recently in the New England Journal of Medicine (September 16, 2016 issue ahead of print). The study population does not include patients requiring emergent surgery, unlike the REVERSE-AD trial. This product will also reverse the effects of indirect factor Xa inhibitors, including LWMH and fondaparinux. A timeline as to when the FDA may approve this product is unknown; the majority of the data with andexanet alfa is with apixaban and rivaroxaban, and the FDA is requiring more information on its effects in patients receiving edoxaban or enoxaparin. An initial IV bolus followed by a subsequent two-hour infusion appears to improve bleeding indices. The product is supplied as a lyophilized powder requiring reconstitution. One major unanswered question is the resulting thrombotic risk in patients, due to rebound increase in anti-Xa activity.[22]

Safety[1-5]

- **Contraindications**: The DOACs are all contraindicated in patients with active pathological bleeding.
- **Black Box Warnings/Precautions**: There is a class Black Box Warning regarding premature discontinuation leading to increased risk of thrombotic events for all the DOACs. Additionally, spinal/epidural hematoma may occur in patients receiving neuraxial anesthesia or undergoing spinal puncture. None of the DOACs should be used in patients with mechanical cardiac valves, due to the risk of valve thrombosis. Edoxaban has a unique warning regarding reduced efficacy in NVAF patients with a CrCl > 95 mL/min; avoid using edoxaban in such patients due to an increased risk of ischemic stroke compared with warfarin, which was found in the ENGAGE trial.
- **Adverse Events:** Bleeding is the main risk with all the DOACS and warfarin; (refer to the previous efficacy sections above for bleeding rates reported in the clinical trials). Dabigatran is associated with more frequent GI complaints, compared to the other products. Dabigatran is poorly bioavailable (6%), and therefore is formulated as a pro-drug (dabigatran etexilate) to enhance absorption; following administration, there is conversion by esterases to the active dabigatran. Dabigatran requires an

acidic environment for absorption, and the capsules contain pellets with a tartaric acid core. The tartaric acid controls the pH to increase absorption, and may contribute to the accounts of dyspepsia associated with dabigatran.

- **End Stage Renal Disease (ESRD) on Hemodialysis:** The package insert for apixaban includes special population information regarding patients with ESRD on hemodialysis. For apixaban, no dose adjustment is necessary except in NVAF patients who are ≥80 years of age or ≤60 kg. The rivaroxaban product labeling also mentions that for patients with ESRD on hemodialysis, a dose of 15 mg QD can be used.
- **Drug Interactions**
  - The extensive drug interactions with warfarin, primarily due to CYP2C9 metabolism, are well known. Additionally, erratic consumption of high-vitamin-K-containing foods can lead to fluctuating INRs. The DOACs have fewer drug interactions than warfarin.
  - A common interaction with both warfarin and the DOACS is an increased bleeding risk when the drugs are taken with concomitant antiplatelets, thrombolytics, or other anticoagulants.
  - Apixaban is primarily metabolized by CYP3A4 and is transported for elimination by P-glycoprotein (P-gp). Strong dual inhibitors of CYP3A4 and P-gp, such as ketoconazole, ritonavir, and clarithromycin, given in combination with apixaban, warrant a dose decrease to apixaban 2.5 mg twice daily. This combination increases exposure to apixaban, increasing the risk of bleeding. Strong dual inducers of CYP3A4 and P-gp, such as rifampin, carbamazepine, and phenytoin, should be avoided. This combination decreases exposure to apixaban, increasing the risk of stroke. Dabigatran, rivaroxaban, and edoxaban are also eliminated via P-gp. Consult the package inserts for dosing recommendations and updated information.
- **Special Populations:** None of the DOACs are approved for use in pediatric patients. Apixaban is the only DOAC with a pregnancy category B rating; dabigatran, edoxaban, and rivaroxaban have pregnancy category C ratings. The pregnancy category B rating with apixaban was not based on clinical trial data, and all the DOACs carry the same wording that there are no adequate and well-controlled studies in pregnant women. The DOACs should not be used in pregnant patients due to risk of pregnancy-related hemorrhage and the absence of an easily administered reversal agent. Warfarin has well-known teratogenic effects and should be avoided in pregnancy. LMWH is preferred for anticoagulation in pregnant women.
- **Discontinuation of Therapy:** Data from the ARISTOTLE trial with apixaban and ROCKET AF trial with rivaroxaban showed an increased risk of stroke ("rebound thrombosis") when the DOAC was discontinued without overlapping with an alternative anticoagulant. Consider administering an alternative anticoagulant if a DOAC must be discontinued for reasons other than active bleeding.

Other Factors

- **Formulations:** Dabigatran capsules should not be split or crushed. Additionally dabigatran must remain in its original packaging, as it degrades when exposed to moisture. Pill boxes to enhance adherence cannot be used with dabigatran.
- **Mandatory Mail:** The branded DOACs are subject to the Mandatory Mail requirements.
- See Table 6 on page 9 for clinical considerations when deciding whether to use a DOAC or warfarin, based on individual patient characteristics.

Conclusion

- The lack of comparative head-to-head trials for the DOACs precludes determining whether one drug will be more effective or safe than another. The individual trial results and individual dosing and pharmacokinetic characteristics of each DOAC must be considered when using these drugs.
- It remains to be determined whether the DOACs will increase the numbers of patients currently undertreated for stroke prevention in NVAF. Also unknown is whether DOACs will improve persistence rates overall for anticoagulation therapy.
- Patients require education and clinical monitoring to ensure appropriate use and avoid adverse reactions with the DOACs. Despite the lack of laboratory monitoring requirements, bleeding is a concern with all the DOACs, and dabigatran is associated with dyspepsia and major GI bleeding.

Table 6: Clinical Considerations of the DOACs versus Warfarin[23]

Patient Characteristic	Preferred DOAC	Rationale and Comments on Warfarin
Increased Risk of GI Bleeding (anemia, hx/o GIB, advanced age, renal dysfunction)	apixaban	• Dabigatran, rivaroxaban, edoxaban associated with increased risk of GIB versus warfarin • Dabigatran associated with dyspepsia • Warfarin: can monitor INR, reverse effects with vitamin K
Increased Risk of Bleeding	apixaban dabigatran edoxaban	• Rivaroxaban showed a trend for increased risk of clinically relevant bleeding versus warfarin • Major bleeding was decreased with apixaban and edoxaban versus warfarin • Dabigatran now has idarucizumab as a reversal agent • Warfarin: can monitor INR, reverse effects with vitamin K
Renal impairment	apixaban	• Apixaban is the least dependent on renal elimination of all the DOACs • Warfarin has no renal elimination
Adherence Issues	edoxaban rivaroxaban	• Only rivaroxaban and edoxaban are dosed daily • Warfarin adherence can be measured with the INR
Drug Interactions	dabigatran edoxaban	• Dabigatran and edoxaban have minimal metabolism through CYP450 pathway • Apixaban and rivaroxaban are substrates of both CYP3A4 and p-glycoprotein, but there is no lab test for the DOACs to monitor for efficacy or safety • Warfarin: can monitor INR for drug interactions • DOACs and warfarin: exercise caution if used with antiplatelets
Pregnancy	None	• LMWHs are drugs of choice in pregnancy • Warfarin is teratogenic; reserve use for women with cardiac valves at high risk of thromboembolism
Pediatrics	None	• No data in children

Adapted from Shapiro NL. American College of Clinical Pharmacy 2016.

References

1. Apixaban (Eliquis) product labeling. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/202155s012lbl.pdf. Accessed November 1, 2016.
2. Rivaroxaban (Xarelto) product labeling. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022406s019s020lbl.pdf. Accessed November 1, 2016.
3. Dabigatran (Pradaxa) package insert. http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022512s028lbl.pdf. Accessed November 1, 2016.
4. Edoxaban (Savaysa) package insert. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/206316s004lbl.pdf. Accessed November 1, 2016.
5. Blank M, McDowell T-Y. Food and Drug Administration: Meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC): October 30, 2014: Edoxaban (Savaysa).
6. January CT, Wann LS, Alpert JS, et al. 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 Practice Guidelines and the Heart Rhythm Society. Circulation. Dec 2 2014;130(23):e199-267.
7. Culebras A, Messe SR, Chaturvedi S, Kase CS, Gronseth G. Summary of evidence-based guideline update: prevention of stroke in nonvalvular atrial fibrillation: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. Feb 25 2014;82(8):716-24.
8. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral Anticoagulation Therapy. Chest 2012;141(2_suppl):e44S-e88S. doi:10.1378/chest.11-2292.
9. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST guideline and expert panel report. CHEST 2016;149(2):315-52.
10. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation (RE-LY). N Engl J Med. Sep 17 2009;361(12):1139-51
11. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation (ROCKET AF). N Engl J Med. 2011;365:883-91.

12. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus Warfarin in Patients with Atrial Fibrillation (ARISTOTLE).
N Engl J Med. 2011;365:981-92.
13. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation (ENGAGE TIMI-22).
N Engl J Med. Nov 28 2013;369(22):2093-104.
14. Garwood CL. Non-vitamin K oral anticoagulants: current evidence and place in therapy. In: 2014 From Theory to Practice: Clinical Reasoning Series in Ambulatory Care Pharmacy. 2014 Oral Anticoagulants: Critical Appraisal of the Evidence and Implications for Patient Care. Lenexa, KS. American College of Clinical Pharmacy, 2014:55-106.
15. van der Hulle T, Kooiman J, den Exter PL, et al. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism:a systematic review and meta-analysis. J Thromb Haemost. 2014;12(3):320-28.
16. Agnelli G, Buller HR, Cohen A, et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism (AMPLIFY). N Engl J Med. 2013;369(9):799-808.
17. Agnelli G, Buller H, Cohen A, et al. Apixaban for Extended Treatment of Venous Thromboembolism. N Engl J Med. 2013; 368(8):699-708.
18. HOKUSAI VTE Investigators. Edoxaban for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013; 369:1406-15.
19. Eriksson BI, Dahl OE, Rosencher N, et al. RE-NOVATE Study Group. Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. Lancet 2007;370:949-56.
20. Eriksson BE, Dahl OE, Huo MH, et al. RE-NOVATE II Study Group. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II). Thromb Haemost 2011;105:721-29.
21. Pollack CV, Reilly PA, Eikelboom JW, et al. Idarucizumab for dabigatran reversal (REVERSE-AD). N Engl J Med 2015;373:511-20.
22. Connolly SJ, Milling TJ, Eeikelboom JW, et al. Andexanet alfa for acute major bleeding associated with Factor Xa inhibitors. (ANNEXA-4) N Engl J Med 2016. DOI: 10.1056/NEJMoa1607887.
23. Shapiro NL, Bhat S. Oral anticoagulants for VTE and stroke prevention in atrial fibrillation. In: Murphy LE, Lee MW, eds. Pharmacotherapy Self-Assessment Program, 2016 Book I. Cardiology. Lenexa, KS: American College of Clinical Pharmacy, 2016;135-52.

Abbreviations

ACC/AHA/HRS	American College of Cardiology / American Heart Association / Heart Rhythm Society
BID	twice daily
CI	confidence interval
CHADS2	congestive heart failure, hypertension, age, diabetes, stroke/transient ischemic attack or thromboembolism
CHEST	American College of Chest Physicians
CrCl	creatinine clearance
DOAC	direct acting oral anticoagulant
DVT	deep venous thrombosis
ESRD	end stage renal disease
GI	gastrointestinal
GIB	gastrointestinal bleeding
INR	International Normalized Ratio
LMWH	low-molecular weight heparin
MI	myocardial infarction
NVAF	non-valvular atrial fibrillation
PE	pulmonary embolism
P-gp	P-glycoprotein
QD	once daily
THR	total hip arthroplasty (replacement)
TKR	total kneed arthroplasty (replacement)
UFH	unfractionated heparin
UF	Uniform Formulary
VTE	venous thromboembolism