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Class Update: Anticoagulants (oral and injectable)

Month/Year of Review: May 2015
Last Review: July 2014
New Drug Evaluation: Edoxaban (Savaysa®)

End date of literature search: March 2015

Dossier Received: Yes

Current Status of PDL Class:

- Preferred Agents: Lovenox® (branded product), dalteparin, unfractionated heparin (UFH), warfarin
- Non-Preferred Agents: enoxaparin, fondaparinux, rivaroxaban, dabigatran, apixaban

Current Prior Authorization (PA): Oral direct thrombin inhibitors (dabigatran) and oral direct factor Xa inhibitors (apixaban and rivaroxaban) are subject to prior authorization criteria to promote safe and effective use among patients requiring anticoagulation.

Research Questions:

- Is there any new evidence of efficacy differences between approved anticoagulants in adults requiring treatment or prevention of deep vein thrombosis (DVT) or pulmonary embolism (PE), orthopedic prophylaxis of venous thromboembolism (VTE), or prevention of stroke or systemic embolism in patients with atrial fibrillation (AF)?
- Is there and new evidence of differences in harms between the available anticoagulants products?
- Are there indications or subpopulations where one agent may be more effective or safer than other available agents?
- What is the evidence of efficacy and safety for edoxaban?

Conclusions:

- Canadian Cardiovascular Society Guidelines strongly recommend the DOAs in preference to warfarin, based on high-quality evidence from primary literature and meta-analyses, for patients with NVAF requiring anticoagulation. [1] This recommendation was based on evidence of non-inferiority to warfarin, with similar or less major bleeding and less risk of intracranial hemorrhage. American Academy of Neurology Prevention of Stroke in NVAF and the European Primary Care Cardiovascular Society (EPCCS) Consensus Guidance on Stroke Prevention in AF (SPAF) recommends all of the oral anticoagulant options, without preference, for patients with NVAF.[2,3] These recommendations were based on evidence from phase 3 trials. [4-7]
- There is moderate strength of evidence of no difference in efficacy between DOAs and standard therapy (enoxaparin and warfarin) in treating VTE, supported by indirect comparisons from four new systematic reviews.[8-11]

- There is moderate strength of evidence from a meta-analysis of 10 randomized controlled trials (RCT) that patients with mild (n=28,971) and moderate (n=11,722) renal insufficiency and AF, acute DVT or PE, or extended treatment of VTE that the DOAs are non-inferior to conventional anticoagulants with similar or less major bleeding or clinically relevant non-major bleeding (CRNM).[12]
- There is low strength of evidence that LMWH are superior to warfarin and placebo for the primary prophylaxis of VTE in patients with cancer.[13]
- Low strength of evidence demonstrated that DOA use in patients with VTE and cancer reduced the incidence of recurrent VTE and major bleeding when compared to conventional treatment of enoxaparin and warfarin.[14]
- There is moderate strength of evidence that edoxaban 60 mg daily and 30 mg daily are non-inferior to warfarin for the prevention of strokes and systemic embolism in patients with NVAF.[7] There is moderate strength of evidence, based on one good quality trial, that edoxaban 60 mg daily is non-inferior to warfarin for the treatment of VTE.[15]. Edoxaban is not recommended for patients with a CrCl >95 mL/min due to enhanced renal clearance, resulting in reduced efficacy in this population.[16]
- Common adverse reactions (≥1%) seen with edoxaban are: bleeding, anemia, rash and abnormal liver function tests.[16] There is moderate strength of evidence that both doses of edoxaban were associated with significantly less major bleeding and intracranial bleeds than warfarin in patients with NVAF and significantly more gastrointestinal (GI) bleeds in the high dose edoxaban group compared to warfarin.[7]

Recommendations:

- Atrial Fibrillation: Recommend removing the PA requirement for the DOAs, which are currently not preferred. Recommend all DOAs equally as an option for patients with NVAF and consider comparative pricing in executive session.
- VTE treatment: Recommend that all DOAs as options for the treatment of VTE and consider comparative pricing in executive session.
- Orthopedic Prophylaxis: Recommend all DOAs approved for orthopedic prophylaxis as options and consider comparative pricing in executive session.

Previous Conclusions:

- The new oral anticoagulants (dabigatran, apixaban and rivaroxaban) have been shown to be superior or non-inferior to warfarin for the prevention of stroke and systemic embolism in patient with NVAF based on high strength of evidence (SOE), however, clinical differences remain small. Guidelines recommend warfarin in preference to the newer agents or offer that patient characteristics and discussion of the risks and benefits of all treatments be the determining factors in anticoagulant selection.[17,18]
- For the treatment of VTE, apixaban demonstrated non-inferiority to conventional therapy in one good quality study with reduced rates of major bleeding (moderate SOE).[19] For extended VTE treatment, dabigatran proved to be non-inferior to warfarin with less risk of major or clinically relevant bleeding and that dabigatran is superior to placebo (NNT 19) but with increased risk of bleeding (moderate SOE).[20,21] Low molecular weight heparins (LMWH) are preferred for long-term VTE prophylaxis in patients with cancer, based on high SOE.[22]
- Meta-analysis data in patients undergoing total hip or total knee surgery that require VTE prophylaxis, demonstrated that factor Xa inhibitors (apixaban and rivaroxaban) reduced the rate of symptomatic DVT to a greater extent than LMWH (4 fewer events per 1000 patients) based on high SOE, with a higher occurrence of major bleeding compared to LMWH (2 more events per 1000 patients treated), based on moderate evidence.[23] There was no significant difference in efficacy outcomes between LMWH and dabigatran 220mg daily (strength not available).
- Based on low strength of evidence, rivaroxaban was shown to be as effective as enoxaparin at day 10 and superior to enoxaparin at day 35 when used for thrombus prevention in patients who were medically ill. Enoxaparin treatment was associated with less risk of bleeding compared to rivaroxaban based on low strength of evidence. There is insufficient evidence for the use of rivaroxaban long-term in this population.[24]

Previous Recommendations:

- Atrial Fibrillation: Recommend warfarin as first-line therapy and offer dabigatran and apixaban as non-preferred agents subject to PA approval. No changes to the PDL are recommended.
- VTE treatment: Recommend warfarin or enoxaparin first line with dabigatran, rivaroxaban and apixaban as non-preferred options if clinical criteria are met. Recommend adding apixaban to current PA criteria as a second line option.
- Orthopedic Prophylaxis: Recommend LMWH as an appropriate first-line treatment option. Recommend rivaroxaban and apixaban as non-preferred options if clinical criteria are met. Recommend adding apixaban to current PA criteria as a second line option.
- Medically Ill: If continued anticoagulation is warranted in medically ill patients recommend warfarin as first-line option. Fourteen day supply of rivaroxaban allows transition to preferred therapy in current PA criteria. No changes to the PDL are recommended.
- Add "difficulty obtaining International Normalized Ratio (INR) monitoring" to questions #5 and #9 in Oral Direct Factor Xa Inhibitors PA criteria, and questions #3 and #8 in Oral Direct Thrombin Inhibitors PA.

Reasons for the Review:

A new factor Xa inhibitor, edoxaban, has received FDA approval for patients with NVAF and for the treatment of DVT and PE. The efficacy and safety evidence for edoxaban will be reviewed. Additionally, as the range of treatment options for patients requiring anticoagulation expands, new evidence becomes available. Data on DOAs continues to evolve with the additional FDA approved indications and additions to the literature. The recent Drug Effectiveness Review Project (DERP) scan will be reviewed with applicable literature added. New indications and safety alerts since the last drug class update in 2014 will summarized.

Background:

Anticoagulants are used in the prevention and treatment of a variety of medical conditions. Thrombosis results from damage to the endothelial lining of blood vessels which trigger activation of the coagulation cascade leading to thrombus formation.[25] Injectable anticoagulants work by enhancing antithrombin (AT) which is responsible for inhibiting a variety of clotting factors.[26] Oral anticoagulants exhibit anticoagulant activity through blocking the formation of vitamin K clotting factors (warfarin), direct thrombin inhibition (dabigatran) or factor Xa inhibition (rivaroxaban, apixaban and edoxaban).[27-30] Commonly used oral and injectable anticoagulants are presented in table 1.

Table 1. Anticoagulants – FDA Approved Indications[16,26-30]

Drug	DVT/PE Prophylaxis	DVT/PE Treatment	Atrial Fibrillation	Cardiac Valve Replacement	Post- MI
Warfarin (Coumadin®)	**+**	**+**	**+**	**+**	**+**
Dabigatran (Pradaxa®)	---	+	**+** (nonvalvular only)	---	---
Rivaroxaban (Xarelto®)	+ (Studied in THR and TKR)	+	+ (nonvalvular only)	---	---
Apixaban (Eliquis®)	+ (Studied in THR and TKR)	+	+ (nonvalvular only)	---	---
Edoxaban (Savaysa®)	---	+	+	---	---
Enoxaparin (Lovenox®)	+	+	---	---	+

* MI- myocardial infarction, DVT – deep vein thrombosis, THR- total hip replacement, TKR- total knee replacement

The most important outcomes in assessing therapy for treatment and prevention of VTE include the occurrence or reoccurrence of VTE, major bleeding and all-cause mortality. Additional relevant outcomes include: minor bleeding, cardiovascular events and withdrawals due to adverse events. Early research relied primarily on symptomatic VTE and fatal PE as measures of antithrombotic prophylaxis efficacy. When evaluating anticoagulation therapies for patients undergoing hip or knee replacement surgeries current literature has incorporated the use of the surrogate outcome, asymptomatic DVT, detected by mandatory venography.[31] The American College of Chest Physicians (ACCP) guidelines find this outcome "fundamentally unsatisfactory" due to the inability to weigh the risks and benefits of efficacy (knowledge of symptomatic events) compared to serious bleeding.[32] The guidelines provide suggestions to estimate reductions in symptomatic thrombosis, dependent upon available evidence. Many studies that evaluate the effectiveness of anticoagulants in surgery patients rely on asymptomatic DVT events to determine treatment differences and are not powered to detect a difference in the frequency of symptomatic events, due to low occurrence rates.[31]

Rates of stroke, systemic embolisms and mortality are appropriate outcomes in evaluating treatment for AF. Secondary outcomes of interest are rates of ischemic and hemorrhagic strokes and incidence of myocardial infarctions (MI). Important safety outcomes include major bleeds, clinically relevant non-major bleeds and GI bleeding.

VTE Prophylaxis

For patients undergoing total hip replacement (THR) or total knee replacement (TKR), prophylactic anticoagulants are considered standard practice. ACCP guidelines recommend the use of LMWHs over other available anticoagulants (moderate evidence).[32] A minimum treatment duration of 10-14 days is recommended (moderate evidence).[32] There is moderate evidence suggesting thromboprophylaxis be continued for up to 35 days from the day of the surgery.[32] The FDA approved doses for subcutaneous enoxaparin prophylaxis in patients undergoing hip replacement surgery is 30 mg every 12 hours or 40 mg once daily and for knee replacement surgery is 30 mg given every 12 hours.[26] This is in contrast to the common European dosing regimen of enoxaparin 40 mg given once daily for prophylaxis in patients undergoing knee replacement, which is used in some trial designs. Guidelines favor LMWH over fondiparinux, apixaban, dabigatran, rivaroxaban or unfractionated heparin (UFH) based on moderate strength of evidence.[32]

For patients who are medically ill and at risk for VTE, prophylaxis is recommended with one of the following therapies; LMWH, UFH or fondaparinux.[32]

Acute VTE Treatment

ACCP guidelines recommend the use of LMWH, fondaparinux, intravenous (IV) UFH or subcutaneous (SC) UFH for the acute treatment of DVT and PE.[32] The treatment duration is indication dependent, however, long-term anticoagulation is recommended, ranging from 3 months to extended therapy.[32] Treatment with vitamin K antagonists (VKA) are recommended over LMWH for extended anticoagulation in most patients (Grade I, low evidence), except those with cancer in which LMWHs are preferred, based on moderate evidence.[32] American Society of Clinical Oncology recommends LMWH over VKAs for long-term anticoagulation, based on strong strength of evidence. Newer oral agents aren't recommended for patients with cancer due to insufficient evidence.[33]

Atrial Fibrillation

Patients with AF are at increased risk of stroke and systemic embolism. Risk estimates are based on the $CHADS_2$ and CHA_2DS_2-VASc Classification Scheme (Table 2).[34] The $CHADS_2$ risk stratification scheme has demonstrated a 2% increase in stroke rate for each one-point increase in score. The $CHADS_2$ system designates intermediate risk to those with a score of 1, lacking a clear risk assessment for those at lowest risk.[35] Those with prior history of prior stroke may have their risk underestimated by $CHADS_2$ classification. The CHA_2DS_2-VASc scoring system has a wider scoring system, which correlates to better predictability of risk in those

with a lower initial stroke risk. CHEST guidelines on antithrombotic and thrombolytic therapy recommend anticoagulation for patients with AF and a $CHAD_2$ score ≥1 and the AHA/ACC/HRS guidelines recommend anticoagulation for those with prior stroke, TIA or CHA_2DS_2-VASc score ≥2.[32,34]

Table2. $CHADS_2$ and CHA_2DS_2-VASc Classification Risk Stratification Scores for Subjects with Non-valvular AF[32,34]

Definition and Scores for $CHADS_2$ and CHA_2DS_2-VASc			
$CHADS_2$ acronym	**Score**	**CHA_2DS_2-VASc acronym**	**Score**
Congestive HF	1	Congestive HF	1
Hypertension	1	Hypertension	1
Age ≥75yr	1	Age ≥75yr	2
Diabetes mellitus	1	Diabetes mellitus	1
Stroke/TIA/TE	2	Stroke/TIA/TE	2
Maximum Score	**6**	Vascular disease (prior MI, PAD, or aortic plaque)	1
		Age 65-75 y	1
		Sex category (i.e., female sex)	1
		Maximum Score	**9**

Treatments used for the prevention of embolic events in patients with AF are: warfarin, dabigatran, apixaban, rivaroxaban and edoxaban. 2014 AHA/ACC/HRS guidelines for the management of patients with AF recommend treatment with warfarin (level of evidence [LOE} A).[34] Dabigatran, apixaban and rivaroxaban are also recommended (LOE B) (edoxaban not approved at time guideline). AHA/ASA guidelines recommend warfarin and apixaban with a LOE A recommendation and dabigatran and rivaroxaban with a LOE B recommendation for patients with stroke or transient ischemic attack.[34]

Methods:

A Medline literature search beginning June 2014 (since last anticoagulant drug class update) and ending February 2015 for new systematic reviews and randomized controlled trials (RCTs) of anticoagulant therapies was performed. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. The primary focus of the evidence is on high quality systematic reviews and evidence based guidelines for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

DERP – Literature Scan of Newer Anticoagulants

In March of this year the Drug Effectiveness Review Project (DERP) released a literature scan of their original drug class review of newer oral anticoagulants.[35] Literature focused on evidence for efficacy and harms of the DOAs in adults with AF, prevention or treatment of VTE in adults who are medically ill or VTE events in adults who have undergone orthopedic surgery. Dabigatran, apixaban, rivaroxaban and edoxaban were included treatments. Data from February 2014 to February 2015 was searched.

Edoxaban was approved in January of 2015 and evidence used for approval will be discussed in the new drug section of this document.

One new head-to-head trial comparing dabigatran (n=30) to rivaroxaban (n=30) in patients undergoing ablation of AF was published.[35] D-dimer levels were measured before the procedure, at the end of ablation and 24 and 48 hours after the procedure. D-dimer levels significantly increased following the procedure in patients taking rivaroxaban compared to patients on dabigatran. The clinical significance of this difference is unknown. A sub-analysis of patients with moderate renal impairment in the J-ROCKET AF trial, which compared rivaroxaban to VKA treatment in Japanese patients, was also reported.[35] Patients with a CrCl 30-49 mL/min were given a reduced dose of rivaroxaban, 10 mg once daily and patients with CrCl > 50 mL/min were given 15 mg once daily. The safety and efficacy of rivaroxaban compared to warfarin was similar in patients with moderate renal impairment and normal renal function. All other evidence presented in the DERP report was previously reviewed in the last DURM anticoagulant class update.

Systematic Reviews:

Sardar, et al. – Novel Oral Anticoagulants in Patients with Renal Insufficiency: A Meta-analysis of Randomized Trials

The focus of the review was to evaluate the efficacy and safety of the DOAs compared to conventional treatment in patients with renal insufficiency in studies with one or more comparators (warfarin or another VKA, LMWH, aspirin, or placebo). DOAS included were dabigatran, apixaban and rivaroxaban.[12] Ten trials satisfied the inclusion criteria, which included patients with AF, acute DVT or PE, or extended treatment of VTE. Patients with severe renal insufficiency were excluded; rivaroxaban and dabigatran studies excluded patients with CrCl <30 mL/min and apixaban trials excluded those patients with CrCl < 25 mL/min. Patients with mild (CrCl 50-79 mL/min) and moderate (CrCl 30-49 mL/min) renal impairment were analyzed.

Patients with mild renal insufficiency (n=28,971) were included in the analysis. Rates of major bleeding or CRNM bleeding was less in patients treated with DOAs compared to conventional treatment (OR 0.81; 95% CI, 0.72-0.90; NNT 143), which was similar for individual treatment comparisons.[12] DOAs were associated with significantly less stroke or systemic embolism than conventional treatments in patients with AF (OR, 0.70; 95% CI, 0.54 to 0.92; p = 0.010, NNT 105). For the prevention of VTE or VTE-related death, the DOAs were non-inferior to conventional treatment. Major and CRNM bleeding was lower with DOAs compared to conventional treatment in patients with AF (OR, 0.80; 95% CI, 0.71 to 0.90) but not in those with acute VTE (OR, 0.85; 95% CI, 0.64 to 1.11).[12] Patients treated with DOAs compared to warfarin were found to have less major and CRNM bleeding but similar rates when compared to LMWH or LMWH followed by VKA.

In over 11,000 patients with moderate renal impairment, (n=11,722), there was no difference in major bleeding or CRNM bleeding in patients taking DOAs compared to conventional treatment when using a random effects model (OR, 0.82; 95% CI, 0.59 to 1.14).[12] Significantly less major bleeding and CRNM bleeding in patients taking DOAs compared to conventional treatment when using a fixed effects model, though a random effects model is more appropriate when assessing rare binary outcomes such as bleeding.[12] DOAs were associated with significantly less risk of stroke or systemic embolism than conventional therapy (OR 0.72; 95% CI, 0.57 to 0.92; NNT 71).[12] VTE and VTE-related death rates were similar for DOAs and conventional therapy. In patients with AF or acute VTE, the risk of major or CRNM bleeding was similar in patients taking DOAs or other anticoagulants. The difference in major or CRNM bleeding was also not significantly different when warfarin, LMWH, LMWH followed by warfarin, aspirin or placebo was compared to DOAs.

Treatment of VTE

Four new systematic reviews indirectly comparing the DOAs in the treatment of VTE have been published since the last review.[8-11] Their findings demonstrate similar efficacy and safety of the DOAs to each other and to standard therapy (LMWH and VKAs). This evidence supports our previous conclusions.

Cochrane - Primary Prophylaxis for Venous Thromboembolism in Ambulatory Cancer Patients Receiving Chemotherapy

A Cochrane systematic review was done to determine the efficacy and safety of LMWHs for primary prophylaxis for VTE in patients undergoing chemotherapy.[13] Twelve randomized clinical trials were identified, involving 9861 patients. Most patients had advanced cancer. The primary outcomes for efficacy and safety were symptomatic VTE and major bleeding, respectively. In a comparison of LMWH to an inactive control and when compared to warfarin, LMWH was associated with a significant reduction in the risk of VTE. However, the differences in rates of VTE were not significant when LMWHs were compared to aspirin. Warfarin was associated with a non-significant decrease in the incidence of symptomatic VTE compared to LMWHs. No major bleeding was reported with LMWH or warfarin and low rates in patients taking aspirin (1%). The risk of major bleeding remains imprecise as data are associated with wide confidence intervals, thus limiting conclusions on safety.

Vedovati, et al. – Direct Oral Anticoagulants in Patients with VTE and Cancer

Ten studies were included in a systematic review of the efficacy of DOAs in patients with VTE and cancer.[14] Six of these studies were included in the meta-analysis for a total of 1132 patients. Drugs included were dabigatran, rivaroxaban, apixaban and edoxaban. All included studies used heparin and VKA combination as a comparator. The primary outcome was recurrent VTE but the rate of major bleeding and CRNM bleeding was also analyzed. The percentage of patients in each trial with cancer ranged from 2.5% to 9.4%. Recurrent VTE rates were lower in patients treated with DOAs compared to conventional treatment of enoxaparin and warfarin (OR 0.63; 95% CI, 0.37 to 1.10).[14] Major bleeding was also lower in patients treated with DOAs compared to conventional treatment, 3.2% and 4.2%, respectively. The DOAs may be a treatment option for patients with VTE and cancer but larger studies are needed.

New Guidelines:

2014 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

The Canadian Cardiovascular Society (CCS) updated their guidelines for AF in 2014.[1] No methodology for guideline development is outlined. The guideline implements a new simplified algorithm for determining appropriate candidates for anticoagulation therapy (Fig 1.). The first recommendation is that all patients with AF or atrial flutter (AFL) should be stratified based on risk of stroke (strong recommendation, high quality of evidence). Oral anticoagulant therapy is recommended for most patients aged ≥ 65 years or CHADS2 score ≥ 1 (strong recommendation, moderate-quality of evidence). Aspirin 81 mg daily is recommended for patients with no risk factors based on the algorithm (conditional recommendation, moderate-quality evidence). No anticoagulation therapy is recommended for patients with no risk factors (conditional recommendation, low-quality of evidence).

For patients with non-valvular AF, whom anticoagulation is indicated, dabigatran, rivaroxaban, apixaban or edoxaban are recommended in preference to warfarin (strong recommendation, high-quality evidence).[1] Dabigatran 150 mg twice daily compared to warfarin appears to be more favorable in patients < 75 years of age but less favorable in those aged ≥ 75 years. Dabigatran 110 mg twice daily is recommended for this older population, however, this dose is not currently available. Dabigatran has been associated with increased gastrointestinal bleeding compared to warfarin. In patients with estimated glomerular filtration rates (eGFR) of 30-50 mL/min/ 1.73 m^2, rivaroxaban or apixaban may be a better option than dabigatran due to less reliance on renal clearance. For patients with mechanical prosthetic valves, rheumatic mitral stenosis or eGFR of 15-30 mL/min/1.73m^2, warfarin is recommended (strong recommendation, moderate-quality of evidence). Patients at risk for stroke who refuse oral anticoagulants should be offered aspirin 81 mg per day with clopidogrel 75 mg daily (strong recommendation, high-quality of evidence). Patients that are candidates for cardioversion should receive at least 4 weeks of an oral anticoagulation

following procedure (conditional recommendation, moderate quality of evidence). Four weeks of anticoagulation is also recommended following immediate electrical cardioversion (strong recommendation, low-quality of evidence).

Fig. 1 Canadian Cardiovascular Society Algorithm[1]

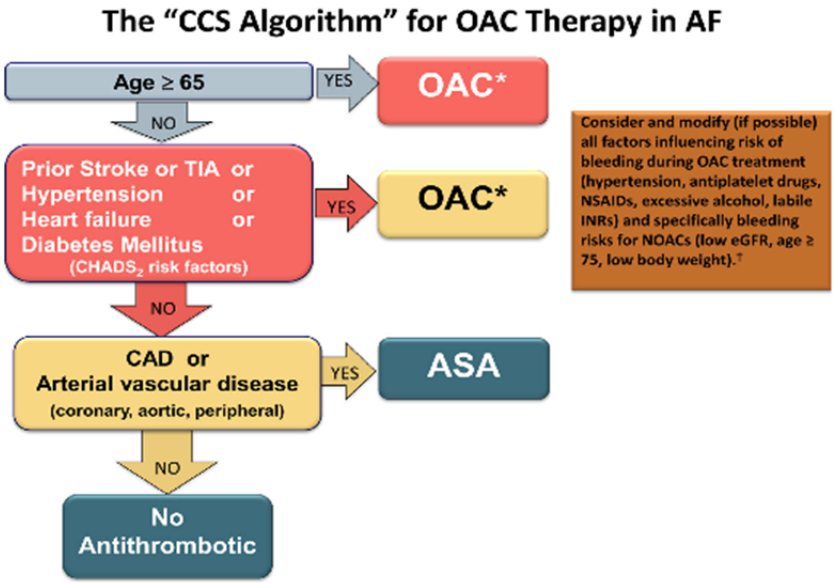

Figure 1. The simplified "CCS algorithm" for deciding which patients with atrial fibrillation (AF) or atrial flutter (AFL) should receive oral anticoagulation (OAC) therapy. * We suggest that a NOAC be used in preference to warfarin for non-valvular AF. † Might require lower dosing. ASA, acetylsalicylic acid; CAD, coronary artery disease; CCS, Canadian Cardiovascular Society; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge, **D**iabetes, **S**troke/Transient Ischemic Attack; eGFR, estimated glomerular filtration rate; INR, international normalized ratio; NOAC, novel oral anticoagulant; NSAID, nonsteroidal anti-inflammatory drug; TIA, transient ischemic attack.

American Academy of Neurology – Summary of Evidence-based Guideline Update: Prevention of Stroke in Non-valvular Atrial Fibrillation

A systematic review of the literature was used to formulate recommendations regarding the prevention of stroke in patients with NVAF.[2] Edoxaban was not included in the recommendations. Recommendations were based on evidence and assigned levels of obligation (A,B,C,U) based on the modified Delphi process. The American Academy of Neurology recommends all patients be informed of increased risk of stroke with NVAF as well as the benefits and risks of treatment of anticoagulants (Level B). Patients with a history of TIA or stroke should be offered anticoagulation on a regular basis (Level B). Patients with low risk of stroke may be offered aspirin or no anticoagulation (Level C). Patients should be stratified by risk to determine the most appropriate patients for anticoagulation treatment (Level B). If anticoagulation is indicated, the following options should be considered based on current labeling: warfarin, dabigatran, rivaroxaban or apixaban (Level B). Patients already well controlled on warfarin should consider staying on warfarin treatment (Level C).[2] Patients with NVAF at higher risk of intracranial bleeding should be considered for dabigatran, rivaroxaban or apixaban therapy (Level B). Apixaban should be considered for patients requiring anticoagulation with a GI bleeding risk (Level C). Dabigatran, rivaroxaban or apixaban should be offered to patients unwilling or unable to submit to INR testing

(Level B). Apixaban should be offered to patients who are not candidates for warfarin treatment (Level B). If apixaban is unavailable, dabigatran or rivaroxaban should be considered (Level C). If anticoagulants are unavailable then aspirin and clopidogrel should be considered (Level C).

European Primary Care Cardiovascular Society (EPCCS) Consensus Guidance on Stroke Prevention in Atrial Fibrillation (SPAF) in Primary Care

The European Primary Care Cardiovascular Society recently updated their 2012 practice guidelines.[3] Recommendations are based on evidence from major clinical trials of DOAs and consensus expert recommendations. Recommendations are based on the NICE format, using wording such as a *strong* or *consider* which are applied to practice guidance. All of the recommendations presented below were strongly recommended.

The guidelines recommend the CHA_2DS_2-VASC scoring system, especially for patients with a $CHADS_2$ score of 1 or less, above the $CHADS_2$ system for determining stroke risk in patients with AF. Patients with a CHA_2DS_2-VASC score of 2 or above should be considered for anticoagulation.[3] Bleeding risks should be discussed with all patients (strong recommendation). Patients with mechanical heart valves or severe valve disease should be treated with a high intensity VKA. Warfarin (INR target of 2.5) or the DOAs should be considered for patients without mechanical valves or clinically significant valve disease. Patients unwilling or unable to take warfarin and patients that are unable to maintain a stable INR should be offered DOAs in preference to warfarin. Treatment adherence and the risks of benefits of treatment should be reviewed with all patients. In patients with a CrCl < 30 mL/min, dabigatran should not be used and factor Xa inhibitors should be used with caution.

NICE Guidance – Dabigatran Etexilate for the Treatment and Secondary Prevention of DVT and/or PE

The National Institute for Health and Care Excellence (NICE) has recommended that dabigatran be an option for treating DVT and PE and preventing recurrent DVT and PE in adults.[36] No specific preference for agents were recommended. This recommendation comes after a review of the primary literature, data submissions by the manufacturer and completion of a technology appraisal guidance.

NICE Guidance - Rivaroxaban for Preventing Adverse Outcomes After Acute Management of Acute Coronary Syndrome

Rivaroxaban with aspirin alone or with aspirin plus clopidogrel is recommended as an option for adults with acute coronary syndrome with elevated biomarkers for the prevention of atherothrombotic events.[37] This recommendation comes after a review of the primary literature and data submissions by the manufacturer and completion of a technology appraisal guidance.

Safety Alerts:

Black box warnings were updated for rivaroxaban on the timing of administration and neuraxial procedures and the risk of spinal/epidural anesthesia or puncture.[36] Apixaban prescribing information was updated with the warning of risk of thrombotic events upon premature discontinuation.[32] A drug safety communication was released for the risk of higher GI bleeding associated with dabigatran.[35]

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including Black Boxed Warning and Risk Evaluation Mitigation Strategies (if applicable), indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:
Edoxaban was approved January 8, 2015 and is indicated for the reduction in the risk of stroke and systemic embolism in patients with NVAF and for the treatment of DVT and PE in patients already treated with 5-10 days of a parenteral anticoagulant.[16]

Non-valvular Atrial Fibrillation
The ENGAGE AF-TIMI 48 was a good quality, double-blind, double-dummy, phase 3 RCT in 21,105 patients with NVAF.[15] Patients were randomized to edoxaban 60 mg once daily (high-dose), edoxaban 30 mg once daily (low-dose) or warfarin (titrated to an INR of 2-3) and treated for a median of 2.5 years.[7] Patients were a median age of 72 years, 38% were female and a majority of patients had a CHADS2 score ≤3. Most common risk factors qualifying patients for treatment were advanced age, congestive heart failure and hypertension. Twenty-eight percent of patients in each group had a prior history of stroke or transient ischemic attack. Twenty-five percent of patients required a dosage reduction at time of randomization and 58% had previously used a VKA for at least 60 days. INRs were measured at least monthly with an encrypted point-of-care device, utilizing sham INR values in the edoxaban group to maintain blinding. The time in therapeutic range (TTR) was 65% for patients being treated with warfarin. The primary end point was a composite of stroke or systemic embolic event. Key secondary end points were all cause mortality and myocardial infarctions. Additional composite endpoints were included in the study, which may overestimate the treatment effect, and therefore are not presented.

High-dose edoxaban was noninferior to warfarin with 182 vs. 232 stroke or systemic embolic events, respectively (HR 0.79; 97.5% CI, 0.63 to 0.99; P<0.001 for noninferiority). Low-dose edoxaban was noninferior to warfarin with 253 events occurring in the edoxaban group compared to 232 in the warfarin group (HR 1.07; 97.5% CI, 0.87 to 1.31; P=0.005 for noninferiorty.[7] The noninferiority delta was set at 1.38 which preserved 50% of benefit of warfarin over placebo. The primary endpoint was driven by ischemic strokes. Hemorrhagic stroke rates were significantly lower in the high-dose and low-dose edoxaban groups compared to warfarin, with 49 events, 30 events and 90 events, respectively. Incidences of ischemic strokes were similar between high-dose edoxaban (n=236) and warfarin (n=235). Low-dose edoxaban was associated with a significantly higher rates of ischemic strokes compared to warfarin, HR 1.41 (95% CI, 1.19 to 1.67; P<0.001). All-cause mortality was significantly lower with low-dose edoxaban group compared to warfarin with an absolute risk reduction (ARR) of 1.0% and number need to treat (NNT) of 100.[15] Myocardial events were not statistically different between groups. Primary outcome event rates were low and similar among groups during the 30-day transition period from randomized anticoagulant to open-label treatment.

Subgroup analyses on efficacy and safety data were predominately similar across subgroups such as $CHADS_2$ score and geographical region.[7] However, patients treated with high-dose edoxaban with a CrCl >95 mL/min had an increased incidence of ischemic stroke compared to warfarin. Therefore, edoxaban is not recommended in these patients. Edoxaban blood levels have been strongly correlated with the effectiveness of edoxaban. Patients previously treated with vitamin K therapy had similar rates of stroke and systemic embolism in both high-dose edoxaban and warfarin groups compared to those patients naïve to vitamin K therapy, who experienced significantly fewer stroke and systemic embolisms with high-dose edoxaban compared to warfarin. Those patients on low-dose edoxaban and amiodarone or aspirin had an enhanced treatment effect compared to patients on low-dose therapy without those agents. Patients requiring a dose reduction of edoxaban demonstrated less bleeding in both edoxaban groups compared to warfarin.

VTE Treatment

Edoxaban 60 mg once daily was compared to warfarin (adjusted to INR 2-3) in a good quality phase 3, double-dummy design, RCT of 8240 patients receiving at least 5 days of enoxaparin for the treatment of VTE.[15] Patients with an estimated CrCl of 30-50 mL/min, body weight of ≤60 kg or use of a potent P-glycoprotein inhibitor received a reduced dose of edoxaban 30 mg once daily. Patients received treatment for 3-12 months, depending upon physician preference. Patient characteristics were the following: 57% males, average age of 56 years, 70% Caucasian and a majority had no VTE risk factors. Forty-one percent of patients presented with PE (with or without DVT) and 59% of patients with DVT only. Patients randomized to receive warfarin had therapeutic INRs 64% of the time. The median treatment duration with enoxaparin was 7 days. The primary endpoint was occurrence of adjudicated symptomatic recurrent VTE, which included DVT or nonfatal or fatal PE. A key secondary endpoint was mortality. Additional composite endpoints were included in the study, which may overestimate the treatment effect, and therefore are not presented.

This study found edoxaban 60 mg once daily was noninferior to warfarin for the treatment of VTE, HR 0.89 (95% CI 0.70 to 1.13; P<0.001 for noninferiority).[15] Candidates for the reduced edoxaban dose of 30 mg once daily experienced the primary endpoint more than those on warfarin (hazard ratio [HR] 0.73; 95% CI, 0.42 to 1.26). Rates of death were similar between groups (3.2% for edoxaban and 3.1% for warfarin). Acute coronary events and cerebrovascular events were not statistically different between the groups. Overall attrition rates in the study were low.

Off-Label Uses

Edoxaban was studied in two poor quality trials in Japanese patients undergoing total knee arthroplasty and hip fracture surgery.[38,39] The dose of enoxaparin and edoxaban were lower than comparative trials due to the lower average body weight of Japanese patients (mean weight 60 kg), making the data less applicable to our fee-for-service population. For these reasons these trials are excluded from the review.

Study Limitations

These studies have limitations, which should be considered. The ENGAGE AF-TIMI 48 trial had a high attrition rate, which was a significant limitation in that trial. Patients taking antiretroviral therapy or cyclosporine were excluded from the VTE trial and therefore the efficacy of edoxaban in this population is unknown. Careful attention needs to be given to the patient's renal function since edoxaban is highly cleared by the kidneys and has reduced efficacy in patients with CrCl >95 mL/min with a 40% reduction in blood levels.

Clinical Safety:

The most common adverse reactions occurring in ≥5% of NVAF patients were bleeding and anemia. In patients with VTE, the most common adverse events (≥1%) were the following: bleeding, rash, abnormal liver function tests and anemia. In the ENGAGE AF-TIMI 48 trial, severe adverse reactions were similar for low and high dose edoxaban and warfarin (37%, 36% and 39%, respectively).[7] Major bleeding was significantly less in patients with AF treated with low dose edoxaban compared to warfarin (HR 0.47; 95% CI, 0.41 to 0.55; P<0.001) and high dose edoxaban (HR 0.80; 95% CI, 0.71 to 0.91; P<0.001).[11] Intracranial bleeding was also significantly less for low and high dose edoxaban compared to warfarin (0.6%, 0.9% and 1.9%, respectively). Gastrointestinal bleeds were similar in low dose edoxaban patients and patients treated with warfarin. High dose edoxaban was associated with significantly more GI bleeds than warfarin (HR 1.23; 95% CI, 1.02 to 1.50; P=0.03; and NNT 167).[7] In patients being treated for VTE, edoxaban was associated with less first major or CRNM bleeding compared to warfarin (8.5% vs. 10.3%, respectively; P=0.004).[15] Major bleeding and serious adverse events were similar in edoxaban and warfarin treated patients with VTE.[15]

Pharmacology and Pharmacokinetic Properties:[16]

Parameter	
Mechanism of Action	Edoxaban is a selective inhibitor of factor Xa and prothrombinase activity and blocks thrombin-induced platelet aggregation
Oral Bioavailability	62%
Distribution and Protein Binding	Distribution is biphasic. In vitro protein binding is 55%
Elimination	Renal 50%
Half-Life	10-14 hours
Metabolism	Hydrolysis to predominately metabolite M-4

Comparative Clinical Efficacy

Clinically Relevant Endpoints:
1) Mortality
2) Thromboembolic events (DVT, PE and stroke)
3) Major Bleeding (intracranial hemorrhage, gastrointestinal, etc.)
4) Myocardial infarctions

Primary Study Endpoints:
1) Stroke or systemic embolism
2) Recurrent symptomatic VTE
3) Composite of symptomatic PE and symptomatic and asymptomatic DVT
4) Major bleeding

Comparative Evidence Table

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes (% of patients /yr)	ARR/NNH	Quality Rating/ Internal Validity Risk of Bias/ Applicability Concerns
1. Giugliano, et al[7] (ENGAGE AF-TIMI 48) RCT, DD, DB, Phase 3, noninferiority study	1. Edoxaban 30 mg daily (E30)* 2. Edoxaban 60 mg daily (E60)* 3. Warfarin** (W) * Dose was halved if estimated CrCl was 30-50 ml/min, body weight of ≤60 kg or use of verapamil, quinidine or dronedarone.	Demographics: Age: 72 years Female: 38% $CHADS_2$ score ≤3: 78% $CHADS_2$ score 4-6: 22% Key Inclusion Criteria: Age ≥21 y; non-valvular AF; $CHADS_2$ ≥2 Key Exclusion Criteria:	ITT: 1.7034 2.7035 3.7036 mITT: 1. 7002 2. 7012 3. 7012 PP: 1. 4616 2. 4529 3. 4506 Attrition: 1. 2309	Primary Endpoint: **Composite of stroke or systemic embolic event:** E30: 253 (3.6%) E60: 182 (2.6%) W: 232 (3.3%) E30 vs. W for noninferiority: HR 1.07 (97.5% CI 0.87 to 1.31) E60 vs. W for noninferiority: HR 0.79 (97.5% CI 0.63 to 0.99)	 NA NA	Major Bleeding: E30: 1.61% E60: 2.75% W: 3.43% E30 vs. W: HR 0.47 (95% CI 0.41 to 0.55) P<0.001) E60 vs. W: HR 0.80 (95% CI 0.71 to 0.91) P<0.001) Any Intracranial bleeding:	 1.82% / 55 0.68% / 147	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Patients were randomized via a central, 24-hour, interactive, computerized response system. Performance: All personal involved in the study were masked to treatment assignment. Double-dummy design and sham INRs were used to conceal study groups. Detection: Outcome assessment was done by committee that was unaware of study assignment. Attrition: Overall attrition was high with 34% off the study drug at the end of the trial and similar between groups but only 245 patients without follow-up data Cox proportional time

	** Titrated to an INR of 2-3 Treatment duration: 2.5 years	- CrCl <30 ml/min - cardiac co-morbidities - dual antiplatelet therapy	(33%) 2. 2415 (34%) 3. 2417 (35%)	**Stroke:** E30: 360 (5%) E60: 281 (4%) W: 317 (5%) **Hemorrhagic stroke:** E30: 30 (0.43%) E60: 49 (0.70%) W: 90 (1.3%) E30 vs. W: HR 0.33 (95% CI 0.22 to 0.50; P<0.001) E60 vs. W: HR 0.54 (95% CI 0.38 to 0.77; P<0.001) **Ischemic stroke:** E30: 333 (4.73%) E60: 236 (3.35%) W: 235 (3.33%) E30 vs. W: HR 1.41 (95% CI 1.19 to 1.67; P<0.001) **Systemic embolism:** E30: 29 (0.41%) E60: 15 (0.21%) W: 23 (0.33%) <u>Secondary Endpoints</u>: **Death any cause:** E30: 737 (11%) E60: 773 (11%) W: 839 (12%) E30 vs. W: HR 0.87 (95% CI 0.79 to 0.96; p=0.006) **Myocardial infarction:** E30: 169 (2.4%)	NS E30 vs. W: 0.9%/111 E60 vs. W: 0.6%/167 E30 vs.W: 1.4%/ NNH = 71 E60 vs.W: NS NS E30 vs. W: 1%/100	E30: 0.26% E60: 0.39% W: 0.85% E30 vs. W: HR 0.30 (95% CI 0.21 to 0.43) P<0.001) E60 vs. W: HR 0.47 (95% CI 0.34 to 0.63) P<0.001) <u>Gastrointestinal bleeding:</u> E30: 0.82%) E60: 1.51%) W: 1.23%) E30 vs. W: HR 0.67 (95% CI 0.53 to 0.83) P<0.001) E60 vs. W: HR 1.23 (95% CI 1.02 to 1.50) P=0.03) <u>Discontinuations due to adverse effects*</u>: E30: 1093 (15.6%) E60: 1204 (17.2%) W: 1168 (16.7%) p-value not reported <u>Serious adverse events*</u>: E30: 2618 (37.4%) E60: 2530 (36.1%) W: 2698 (38.5%) p-value not reported	0.59%/ 170 0.46%/ 217 0.41%/ 244 NA	to event hazards ratio used to deal with missing data. mITT was appropriately used for non-inferiority analysis and ITT was used for superiority analysis. Non-inferiority delta was set at 1.38 which preserved 50% of benefit of warfarin over placebo. **Applicability**: <u>Patients</u>: A majority of participants had comorbidities: hypertension 94%, CHF 57%, diabetes 36%, and prior stroke 28%. Twenty-five percent required dose reduction at randomization. Fifty-nine percent had received previous VKA therapy. <u>Intervention</u>: Edoxaban 60 mg daily and edoxaban 30 mg daily. Approximately 25% of edoxaban patients required dose reduction primarily due to reduced renal function. <u>Comparator</u>: Time in therapeutic range was a median of 68% and a mean of 65% for patients taking warfarin. <u>Outcomes</u>: stroke and systemic embolism is an appropriate outcome to establish efficacy in patients with AF. Composite outcomes may overestimate treatment effect. <u>Setting</u>: Forty six countries and 1393 outpatient centers. **Analysis**: In patients with a moderate risk of stroke due to AF, high-dose edoxaban was noninferior to warfarin with less major and intracranial bleeding. Low-dose edoxaban was found to be non-inferior to warfarin by a small margin, with less major and intracranial bleeding.

				E60: 133 (1.9%) W: 141 (2.0%)	NS	* Events not annualized		
2. Hokusai-VTE Investigators[15] RCT, DB, DD, noninferiority, Phase 3 3-12 months treatment 12 months follow-up	1. Edoxaban 60 mg daily (E60)* 3. Warfarin** (W) All patients received at least 5 days of enoxaparin or unfractionated heparin. Median duration of treatment with heparin was 7 days. * Dose was halved if estimated CrCl was 30-50 ml/min, body weight of ≤60 kg or use of potent P-glycoprotein inhibitors. ** Titrated to an INR of 2-3 Follow-up median 9 months	Demographics: Age: 56 years Men: 57% Unprovoked DVT or PE: 65% CrCl ≥30 to ≤50 ml/min: 7% Key Inclusion Criteria: Age ≥18 y; Objectively diagnosed acute, symptomatic DVT or PE Key Exclusion Criteria: - CrCl <30 ml/min; Therapeutic heparin >48 h; - Received >1 dose of VKA - Cancer with indication for long-term LMWH - Additional indication for warfarin therapy - ASA >100 mg/day - dual antiplatelet therapy - CrCl <30 ml/min	ITT: 1.4143 2.4149 mITT: 1. 4118 2. 4122 PP: 1. 3937 2. 3955 Attrition: 1. 181 (4.4%) 2. 167 (4.1%)	Primary Endpoint: Recurrent symptomatic VTE: E60: 130 (3.2%) W: 146 (3.5%) HR 0.89 (95% CI 0.70 to 1.13; P<0.001 for non-inferiority) Secondary Endpoints: All Cause Mortality: E60: 132 (3.2%) W: 126 (3.1%) CIs or p-value not reported	NA NA	First major or clinically relevant nonmajor bleeding: E60: 349 (8.5%) W: 423 (10.3%) HR 0.81 (95% CI 0.71 , 0.94) P=0.004 for superiority Major Bleeding: E60: 56 (1.4%) W: 66 (1.6%) HR 0.84 (95% CI, 0.59 to 1.21; P=0.35 for superiority) Serious Adverse Events: E60: 503 (12.2%) W: 544 (13.2%) p-value not reported Discontinuations due to adverse effects: E60: 121 (2.9%) W: 105 (2.5%) p-value not reported	1.8% / 56 NS	**Quality Rating**: Good **Internal Validity (Risk of Bias)**: Selection: Web-based system with stratification according to diagnosis, edoxaban dose and temporary risk factors. Performance: Double-dummy design and sham INRs were used to conceal study groups. Detection: Outcome assessment was done by a committee that was unaware of study assignment. Attrition: Attrition was low overall (4%). mITT analysis with LOCF and Cox proportional hazards model were used for primary outcome. Non-inferiority delta set at HR=1.5 which corresponds to 70% of treatment effect of warfarin. **Applicability**: Patients: Sixty-five percent of patients had an unprovoked VTE. A majority (70%) of patients were Caucasian. Patients were treated for a median of 9 months. Time in therapeutic range was 64% for patient taking warfarin. Intervention: Edoxaban 60 mg daily. Comparator: Warfarin titrated to INR of 2-3. Time in therapeutic range was 63.5%. Outcomes: Recurrent VTE is an appropriate outcome for this indication. Setting: Patients were enrolled from 439 centers and 37 countries. Eighty-seven percent of patients were enrolled in US sites. **Analysis**: In patients with symptomatic DVT or PE, initially treated with a heparin, edoxaban was noninferior to warfarin with less major or clinically relevant nonmajor bleeding.
Abbreviations [alphabetical order]: ARR = absolute risk reduction; CI = confidence interval; CrCl = creatinine clearance; DB = double-blind; DD = double-dummy; DVT = deep vein thrombosis; FAS = full analysis set; INR = international normalized ratio; ITT = intention to treat; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number								

needed to treat; PE = pulmonary embolism, PP = per protocol; VKA = vitamin K antagonists

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Appendix 1: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SAVAYSA™ safely and effectively. See full prescribing information for SAVAYSA.

SAVAYSA (edoxaban) tablets for oral use
Initial U.S. Approval: 2015

WARNING (A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CREATININE CLEARANCE (CRCL) > 95 ML/MIN
(B) PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS
(C) SPINAL/EPIDURAL HEMATOMA
See full prescribing information for complete boxed warning.
(A) REDUCED EFFICACY IN NONVALVULAR ATRIAL FIBRILLATION PATIENTS WITH CRCL > 95 ML/MIN: SAVAYSA should not be used in patients with CrCL > 95 mL/min. In the ENGAGE AF-TIMI 48 study, nonvalvular atrial fibrillation patients with CrCL > 95 mL/min had an increased rate of ischemic stroke with SAVAYSA 60 mg once daily compared to patients treated with warfarin. In these patients another anticoagulant should be used (5.1).
(B) PREMATURE DISCONTINUATION OF SAVAYSA INCREASES THE RISK OF ISCHEMIC EVENTS: Premature discontinuation of any oral anticoagulant in the absence of adequate alternative anticoagulation increases the risk of ischemic events. If SAVAYSA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant as described in the transition guidance (2.4, 5.2, 14).
(C) SPINAL/EPIDURAL HEMATOMA: Epidural or spinal hematomas may occur in patients treated with SAVAYSA who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures (5.4).

INDICATIONS AND USAGE

SAVAYSA is a factor Xa inhibitor indicated:
To reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF) (1.1)

- *Limitation of Use for NVAF*
  SAVAYSA should not be used in patients with creatinine clearance (CrCL) > 95 mL/min because of increased risk of ischemic stroke compared to warfarin at the highest dose studied (60 mg) (1.1)

SAVAYSA is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant (1.2)

DOSAGE AND ADMINISTRATION

- Treatment of NVAF:
  Assess CrCL before initiating therapy (2.1)
  The recommended dose is 60 mg once daily in patients with CrCL >50 to ≤ 95 mL/min. Do not use SAVAYSA in patients with CrCL > 95 mL/min (2.1)
  Reduce dose to 30 mg once daily in patients with creatinine clearance 15 to 50 mL/min (2.1)

- Treatment of DVT and PE:
  The recommended dose is 60 mg once daily (2.2)
  The recommended dose is 30 mg once daily for patients with CrCL 15 to 50 mL/min or body weight less than or equal to 60 kg or who use certain P-gp inhibitors (2.2)

DOSAGE FORMS AND STRENGTHS

- Tablets: 60 mg, 30 mg, and 15 mg (3)

CONTRAINDICATIONS

- Active pathological bleeding (4)

WARNINGS AND PRECAUTIONS

- Bleeding: Serious and potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss (5.2)
- Mechanical heart valves or moderate to severe mitral stenosis: Use is not recommended (5.5)

ADVERSE REACTIONS

Treatment of NVAF: The most common adverse reactions (≥ 5%) are bleeding and anemia (6.1)
Treatment of DVT and PE: The most common adverse reactions (≥ 1%) are bleeding, rash, abnormal liver function tests and anemia (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Daiichi Sankyo, Inc. at 1-877-437-7763 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Anticoagulants: Avoid concomitant use (7.1)
- Rifampin: Avoid concomitant use (7.2)

USE IN SPECIFIC POPULATIONS

- Nursing mothers: Discontinue drug or discontinue nursing (8.3)
- Impaired renal function (CrCL 15 to 50 mL/min): Reduce dose (2.1, 2.2, 8.6)
- Moderate or severe hepatic impairment: Not recommended (8.7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

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